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PASSIVE TRANSFER IN LIGHT URTICARIA

PATHOMECHANISM OF PHYSICAL ALLERGY

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CASE REPORT

A 44-YEAR-OLD shoemaker has been sensitive to light for eighteen years. In summer and also in winter when exposed to snow and sunshine, the uncovered parts of his body, especially the hands and face, become swollen and red. He then has in addition malaise and dizziness. In summer when bathing great swelling of the legs occurs. He knows of no similar case in his family, nor of any allergic history. He had suffered from nephrolithiasis for 10 years until he was operated upon two months prior to admission. After operation he developed erysipelas. His Wassermann reaction was negative.

Examination on April 15, 1940, revealed a short, well-nourished man with white skin, dark eyes and hair. On areas of the skin exposed to light there arose a sharply limited wheal preceded by itching and hyperemia and surrounded by a broad hyperemic areola. On irradiation of larger areas first wheals of various size occurred which soón became confluent, and then an edematous swelling of the whole corium ensued. The hypersensitivity was present on the whole body. Some parts as the limbs, however, were less sensitive than others. The threshold value of wheal formation was determined with a mercury vapor lamp, type Jesionek, 50 cm. distance, five seconds' exposure (on the thigh, fifteen seconds). Thus, the threshold value was from 50 to 60 times less than normal. The early urticarial reaction was not followed by later inflammation, erythema, or pigment formation except when the irradiation reached the usual erythema doses of four to five minutes. Thus he responded to the erythema and pigment-forming rays in a normal manner. Irradiation on the back through the usual fenestrated equipment for from one-fourth to two minutes caused a hyperemia at the end of the second minute. Edema first occurred at the two-minute fenestra but soon, in full accordance with the openings, typical wheals with sharp borders without projections arose at all places surrounded by a confluent hyperemic area (Fig. 1).

It would be important to know exactly the wave length of the rays to which the patient reacts. In want of the proper filters this examination could not be finished. Thus far the following has been established.

From the dermatologic department of the Count Apponyi Policlinic, Budapest. Physician-in-chief: Prof. dr. L. Török.

(1) The patient most readily responds to the colorless mixed light from the sun, also diffuse sunlight, or light from a mercury vapor lamp. No reaction occurs to a strong incandescent lamp (Nitraphot), a carbon arc lamp of little potency, or to "Sollux" and "Vitalux." He does not respond to infrared rays whether from special IR irradiating sources or from a mercury lamp equipped with a filter (Lifa) transmitting IR rays. The patient receives from these sources of light, such as Vitalux, a transient diffuse erythema, but neither a wheal nor a late erythema ensues. (2) The patient responds to blue rays when using a light blue filter. With a dark blue one no reaction occurs. (3) Perhaps he reacts to ultraviolet rays (UV) with the greatest wave length, but no wheal arises with a Wood filter (3,600 A°). He responds to blue but to no other color (Kodak and Lifa filters). In contradistinction to this, a strong irradiation with a mercury vapor lamp at 20 cm. for two minutes brings about urticaria even when the rays are transmitted through thick window panes (up to 8 mm.) impervious to UV rays.

Fig. 1.

He showed a strange behavior to x-rays. On 30 r with 1 mm. aluminum filter or without it he reacted after two days with a slight redness and after four days with a pale pigmentation entirely corresponding to the irradiated quadrangle. There was no early reaction. The pigmentation persisted for a long time.

We cannot yet explain the slight contradictions of this behavior. The analysis of the spectra of the light sources has shown the continu-

ous spectrum of the sun to range to about 2,900 A°, the likewise continuous one of the Vitalux lamp to about 2,700 A°, whereas the linear spectrum of the mercury vapor lamp goes below 2,500 A° with a maximum intensity at 3,663, 3,132 and 4,359 A°. Visible rays are emitted by each. As whealing was produced in the patient also through thick glasses retaining UV-rays and by blue light (4,920-4,240 A°) whereas none arose when the Wood filter (3,660 A°) was being used, it seemed probable that the urticaria was elicited by the rays between 4,000 and 5,000 A° in accordance with the data of the literature (Table I) and occasionally by the wave length 4,359 A° lying in the blue spectrum and abundantly emitted by the mercury vapor lamps. Special antagonistic effects might have accounted for the fact that the wheal could be produced by sunlight and mercury lamp but not by Vitalux having a spectrum resembling the two others. A similar antagonism is known to exist between the UV and the IR radiation. Moreover, the distribution of the ray energy may account for the difference.

In physical allergy a hemoclastic crisis and general symptoms occur, as a rule. In our case a marked though not strong general response was likewise present. After a one-minute irradiation of the whole back which was followed by an edematous swelling of the entire irradiated area, a sensation of heat and weight in the head occurred. There was almost no change in the pulse; the systolic blood pressure became 10 mm. lower; the temperature was unchanged; the leucocyte count diminished from 7,300 to 6,000; the serum refraction value became 20 units higher; the blood clotting time was three minutes longer; and the complement titer was slightly reduced.

We ascribed great importance to the passive transfer test. In the literature there is no report on a positive Prausnitz-Küstner reaction with photogenous urticaria. Only Bernstein in 1933 reported positive transfer to guinea pigs and mice in the form of dermatitis and necrosis (Table III). In our case the transfer was successful several times in the classical form, i.e., by intradermal injection of the patient's serum followed, after twenty-four hours, by irradiation with suberythema-erythema doses. At the site inoculated with the patient's serum, hyperemia appeared with strong itching and then a typical urticaria developed, whereas the place inoculated with the control serum showed no reaction (Fig. 2). Both the sera taken before and after irradiation gave positive tests. The result with the latter was, however, more intensive. The irradiation instituted in the first hours subsequent to the serum injection gave a negative result, in full accordance with the hypothesis that the reagins have to enter the cells and become cell-fast before the allergic reaction occurs. For this process a certain time is

TABLE I

CASES OF PHOTOGENOUS URTICARIA SOLARIS

NO.	AUTHOR	YEAR	CASE	AGE AND SEX	ELICITING RADIATION	POR-PHYR.	LITERATURE
1	Merklen	1904	1	?			Prat. Dermat. **4**: 741
2	Ward, S. B.	1905	1	?			Cit. Duke
3	Ochs, B. F.	1910	1	?			Cit. Duke
4	Duke, W. W.	1923	1	43, ♀	Sun, nitrogen lamp blue violet rays, UV Ø, urt. aft. 2½ min.	Neg.	J. A. M. A. **80**: 1835 J. A. M. A. **83**: 3
5	Beinhauer, L. G.	1925	1	20, ♂	UV rays, Wood light too, merc. vap. lamp 20 cm.-30 sec., IR, visible light Ø	Neg.	Arch. Dermat. **12**: 62
6	Frei, W.	1925	1	25, ♂	Short wave visible, long UV rays, sun 1 min., UV 50 cm.-1 min.	Neg.	Arch. f. Dermat. **149**: 124
7	Cummins	1926	1	28, ♀	Sun, merc. vap. lamp	–	Arch. Dermat. **13**: 419
8	Vallery-Radot, Blamoutier, Besançon, and Saidman	1926	1	42, ♀	Sun from 4,600 to 5,500 A° UV Ø	Neg.	Bull. soc. méd. Hôp. **42**: 1116
9	Vallery-Radot, Blamoutier, Stehelin, and Saidman	1928	1	43, ♀	Violet and red rays, sun 5 min., UV Ø, IR Ø	?	Bull. soc. méd. Hôp. **44**: 1122
10	Flandin and Laubry	1928	1	40, ♀	Red and IR rays!	?	Bull. soc. méd. Hôp. **44**: 1122
11	Wucherpfennig, V.	1928	3	3, ♀ One of them 46 yr.	Visible short wave, UV long wave section, also Sollux and Wood light. Merc. vap. lamp 50 cm., 37 sec.	Neg.	Arch. f. Dermat. **156**: 520

12	Gougerot, Meyer, et Peyre	1929	1	29, ♀	Sun, UV rays of merc. vap. lamp, incandescent light Ø	?	Arch. derm. syph. Hôp. St. Louis **1**: 799
13	Goldschlag, F.	1929	1	58, ♀	Sun, merc. vap. lamp. Sun 2-10 min.	-	Zentralbl. Hautkrkh. **31**: 298
14	Goldschlag, F.	1930	1	45, ♀	Mainly sun, also UV.	Neg.	Zentralbl. Hautkrkh. **34**: 200
15	Glaubersohn and Goldenberg	1930	1	33, ♀	Sun, merc. vap. lamp	-	Dermat. Wehnschr. **2**: 1625
16	Sellei and Liebner	1930	1	52, ♀	Sun, merc. vap. lamp. Yellow and red light. Blue and green Ø	Neg.	Arch. f. Dermat. **161**: 32 Zentralbl. Hautkrkh. **34**: 405
17	Urbach, E.	1931	1	16, ♂	Sunlight, 15 min.	?	Zentralbl. Hautkrkh. **37**: 36
18	Weiss, E.	1932	1	42, ♂	Sun, merc. vap. lamp.	Neg.	J. ALLERGY **3**: 192
19	Urbach, E.	1933	1	39, ♀	Sun, merc. vap. lamp. Yellow, bluish green and UV light	Sometimes	Zentralbl. Hautkrkh. **46**: 293
20	Bernstein, F.	1933	1	40, ♀	Sun, merc. vap. lamp UV section. Sollux Ø. Kromayer compression 1 sec.	Neg.	Arch. f. Dermat. **168**: 177
21	Kissmeyer, A.	1933	1	9, ♀	Sunlight.	-	Zentralbl. Hautkrkh. **45**: 150
22	Blum, H. F., Allington, H., and West, R. J.	1935	1	21, ♂	Sun, Mazda lamp 4,000 to 5,000 A°. UVØ	Neg.	J. Clin. Investigation **14**: 435; **16**: 261, 1937
23	Epstein, St.	1935	1	30, ♀	Short wave sunlight: 4,000 to 4,500 A°. Long wave UV rays?	-	Arch. f. Dermat. **173**: 181, 1936
24	Epstein, St.	1939	1	6, ♂	Short wave sunlight, long wave UV rays	-	Arch. Dermat. **39**: 225
25	Rajka, E.	1940	1	44, ♂	Sun, merc. vap. lamp/30 cm., 5 sec./, blue rays. Wood light, IR Ø	Neg.	Zentralbl. Hautkrkh. **65**: 197

Total: 27 cases (17 women), 32 authors or co-workers.

needed. With urine the transfer did not succeed. It seemed likely that the reagins became partly fixed or, more correctly, inactivated in the patient's serum previously exposed to light. Therefore the transfer was on several occasions made with both irradiated and nonirradiated serum kept in the dark. The passive transfer test was in both cases positive, but the wheal arising at the site injected with irradiated serum was considerably smaller. Once on transferring forty-eight hours after irradiation only a slight redness arose at the site of the irradiated and a typical wheal at that of the nonirradiated serum. We tried also the inversed transfer as suggested by Kenedy, i.e., starting with the irradiation and injecting patient's serum which had been proved to contain reagins immediately thereafter, one-half hour later, and the next day, respectively. In these instances the results obtained were negative.

TABLE II

	A°			
	6,000-5,000	5,000-4,000	4,000-3,000	
Sunshine	43.5	41.6	14.9	per cent
Mercury vapor lamps	28.3	13.9	37.4	
Incandescent lamps with metallic wire (Sollux, Vitalux)	63.5	25.0	11.5	

The following are some excerpts of the records.

April 15, 1940.—Blood was withdrawn: serum I.

April 17.—Irradiation on the back with a lamp, type Bach at 50 cm. for two minutes. Blood taken after twenty minutes: serum II. Transfer to the back of three test persons with P.-K. method. The patient's serum and normal serum (0.1 c.c. each) were injected.

April 19.—Irradiation with Jesionek's lamp at 50 cm. for five minutes. Sites of serum I: in one, no response; in the other two, wheals 8 to 9 mm. with a hyperemic area of 15 mm. Sites of serum II: in one, follicular edema; in the two others, larger wheals measuring from 10 to 11 mm. and a broad hyperemic area. All wheals were itching. At the sites of the control sera no response. Positive P.-K. tests: early reaction with wheals, mainly with the post-irradiation serum. No late reaction at the place of the injection, only a slight erythema on the back of the test persons.

April 30.—Irradiation with Jesionek lamp, blood taken after fifteen minutes: serum III. One part of the serum was kept in dark; the other was irradiated (Bach lamp, 20 cm., six minutes). The control serum was treated in a similar manner.

May 2.—Transfer to five test persons.

May 3 and 4.—(Table IV).

No reaction occurred at the places of the control serum whether irradiated or not. Thus hypersensitiveness to light could be transferred in twelve instances with the method of passive transfer.

We had only a partial success in specific desensitization. When the wheal had been elicited one day over a rather large area, the same area reacted to a similar dose for the next two to three days with only a

hyperemia and at most a minimal nonconfluent edema. Places with pigmentation displayed a lessened sensitivity, e.g., the threshold rate was on the slightly pigmented skin of the forearm from fifteen to thirty-five seconds compared to five seconds, and only hyperemia and follicular edema ensued. At places with x-ray pigmentation only a similar response could be elicited on irradiation lasting as long as one minute. First the patient was treated with resorcinol by mouth and by autourotherapy. Later he took sun baths and nicotinic acid. At the first exposure his limbs became greatly swollen, but, after the edema had passed away in one to two hours, he felt rather well. Later, only a redness of the free areas ensued without swelling. He gradually developed pigmentation and became bronze colored by the end of the summer. At these areas no urticaria could be brought about; only the covered areas, such as the groin, with deficient pigmentation remained sensitive.

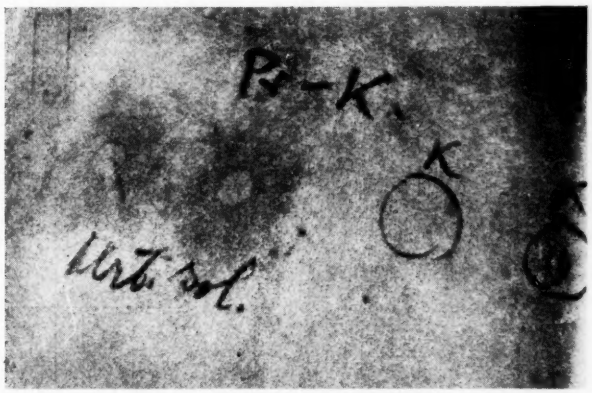

Fig. 2.

For the sake of comparison twenty-seven cases of light urticaria reported by twenty-two authors have been collected from the literature available (Table I). The prevalence of the female sex (seventeen) is striking. This might perhaps be explained by endocrine conditions, as sensitivity to light frequently was increased with menstrual disorders. Noteworthy also is the various duration of the condition ranging from a very short time to many years. Nearly all of the patients reported reacted to the short wave visible (blue) rays and to the long wave UV rays. Exceptionally a patient (2. of Vallery-Radot) responded to the rays ranging from violet to red, that of Sellei and Liebner to yellow-red light, and the one of Flandin to red and IR rays. There were differences as to the pure UV light; the patients of Beinhauer and Wucherpfennig reacted also to the Wood light while that of Rajka did not, and those of Duke and Vallery-Radot did not react to the other UV rays.

TABLE III

	PHYSICAL ALLERGY	AUTHOR	YEAR	METHOD	FORM OF TRANSFER	CASE	REMARKS	LITERATURE
				A. Mechanic				
1	Urticaria factitia	Walzer, A.	1928	Pr-K*	Early reaction	1		Arch. Dermat. **18:** 868
2		Lehner and Rajka	1929	Pr-K	Early reaction	3	Twice dereagin too	Arch. f. Dermat. **159:** 172
3		Gay Prieto, J.	1932	Pr-K	Early reaction	1		Zentralbl. Hautkrkh. **43:** 281
4		Tosatti, P. M.	1936	Pr-K		1		Policlin. Sez. med. **43:** 205
Total						6		
				B. Thermic				
5	Cold urticaria	Lehner, E.	1928	Pr-K and L-R†	Early-late r.	1	With serum postirritation stronger!	Zentralbl. Hautkrkh. **29:** 492a Klin. Wchnschr. 1929. I. 306
6		Liebner, E.	1929	Pr-K	Early r.	1	With serum postirritation stronger!	Zentralbl. Hautkrkh. **34:** 406
7		Harris, K. E., Lewis, Th., and Vaughan, J. M.	1929	Pr-K	Early r.	2		Heart **14:** 305
8		Covisa, J. S., and Gay Prieto	1930	Pr-K	Early r.	2		Dermat. Wchnschr. **2:** 1188
9		Lehner, E.	1931	Pr-K	Early r.	1	Dereagin too	Zentralbl. Hautkrkh. **41:** 199
10		Bernstein, F.	1932	Pr-K	Early r.	3	Reagin inactivable in vitro by cold	Dermat. Ztschr. **64:** 242
11		Weissenbach, R. J., and Brisset, J. P.	1932	Pr-K	Early r.	1	With serum postirritation stronger	Ann. méd. **32:** 333
12		Affolter, J.	1933	Pr-K	Early r.	1	After irritation positive	Schweiz. med. Wchnschr. **2:** 881

13		Kambayashi, T.	1933	Guinea pig	Arthus phen.	1		Zentralbl. Hautkrkh. **46:** 55
14		Rikimaru, H.	1934	L-R	Late r.	2		Zentralbl. Hautkrkh. **50:** 393
15		Benjamins, C. E.	1934	Pr-K	Early r.	1		Nederl. Tijdschr. Geneesk. 1934, 5362
16		Bodenstein, E.	1934	Pr-K	Early r.	2		Zentralbl. Hautkrkh. **52:** 364
17		Pernyés-Pietsch (Rothman St.)	1937	Pr-K	Early r.	1	After irritation positive	Zentralbl. Hautkrkh. **56:** 8
Total						19		
18	Heat urticaria	Lehner and Rajka	1929	Pr-K	Late r.	1	With serum postirritation stronger	Krankh. frschg. **8:** 85
19		Kambayashi, T.	1933	Guinea pig	Arthus phen.	1		Zentralbl. Hautkrkh. **46:** 55
20		Richter, W.	1935	Pr-K	Early-late r.	1	Reagin inactivated by heat in vitro	Dermat. Wchnschr. **1:** 129
21		Melczer, N., and Wlassics, T.	1937	K-U‡ and L-R	Late r.	2	Pr-K neg.! 1 case exhaustion urt. Pos. transfer by heat!	Arch. f. Dermat. **176:** 157
Total						5		
				C. Light				
22	Urt. photogenica	Bernstein, F.	1933	Guinea pig and white mouse	Late r. (necrosis)	1	Pr-K neg.! Porphyrine neg.	Arch. f. Dermat. **168:** 177
23		Rajka, E.	1940	Pr-K	Early r.	1	Porph. neg. With serum postirritation stronger. Reagin inactivated by light in vitro	Zentralbl. Hautkrkh. **65:** 197
24	Light dermatitis	Rajka, E.	1930	Pr-K	Late r.	1	Porph. neg. Artificial sensitization?	Zentralbl. Hautkrkh. **34:** 405
25		Callaway, J. L.	1940	Pr-K	Late r.	1	Coproporph. I increased. No difference with irradiated serum	Arch. Dermat. **41:** 889
26	Bullous photodermatitis	Flarer, F.	1930	K-U	Late r.	2	Porph. neg.?	Arch. ital. Dermat. **5:** 543
Total						6		
						36		

*Praussnitz-Küstner reaction.
†Lehner-Rajka reaction, transfer to rabbit ear.
‡Königstein-Urbach reaction with the content of the vesicle induced over the allergic skin area.

The remaining cases recorded seemingly belong to or are partly united with the group of light urticaria and are probably erythematous, eczematous or pruriginous photodermatoses partly termed by Haussmann and Haxthausen as polymorphous photodermatoses. Jausion and recently Epstein were concerned with these pathologic pictures. These patients react to a light test with a late rather than early reaction lasting for several days, as a rule, with a more or less edematous-urticaria appearance. Their boundary in contrast to the genuine light urticaria no doubt is not sharply drawn, whereupon various transitory and compound forms exist. Epstein reported a case reacting to weak exposure with a wheal, and to a stronger one with an acute dermatitis and prurigo on the arms. Barber, Darier, Jausion, Rost, and Keller believe that photogenous urticaria, eczema *solare* and prurigo *aestivalis* form one group with each element closely related to one another. The majority of the patients are likewise women with frequent menstrual disorders and, in the cases of Barber and Howitt, and of Urbach, with a change of the enteric bacterial flora—dysbacteriosis. The vast majority react similarly to the short wave section of the visible and the long wave section of the UV rays. In the patients of Callaway, Flarer, and Rajka, the passive transfer test was positive (Table III). These pictures are much more frequent than the genuine light urticaria. Haxthausen reported thirty similar cases; Jausion, five; Sellei and Liebner, seven; Duke, Charbonnier and Drouet, D'Amato, Schmidt-La Baume, and Bernstein, one case each. In most instances no photocatalysator could be found. In the dysbacteric patients the porphyrine of the feces was elevated but that of the urine was not. In Callaway's case there was increased coproporphyrine I in the urine pointing to a pathologic (congenital?) porphyry. The investigations of Brunsting, Brugsch, and O'Leary have shown the urinary coproporphyrine output in twenty-four hours to be usually normal in the patients suffering with solar eczema or urticaria.

In our case of light urticaria whealing could, by small ray doses, be developed and was accompanied by general symptoms and a hemoclastic crisis. The passive transfer was positive and specific desensitization partly succeeded. Thus, we feel warranted in believing this case to be one of genuine physical allergy. At an earlier time much difficulty arose from grouping together physical allergy and true allergic diseases because it was not easy to realize an allergen-reagin reaction having as one factor a physical agent. The presumption of a secondary endogenous allergen substituting for the physical one and acting like a hapten does not, although it has been much advocated, give a satisfactory explanation. First of all the successful passive transfer renders the role

of a secondary specific allergen superfluous. Concerning the latter, it might be assumed that it is not constantly circulating in the patient's blood but is formed only periodically under the action of the physical stimulus. When using for the transfer test a serum withdrawn from the patient before the influence of the irritation, one finds that such serum contains no secondary allergens and only reagin is present. The physical stimulus administered to the test person twenty-four hours later encounters only reagins but no specific secondary allergen, as this is not produced in the normal skin. Nevertheless passive transfer is positive. Should a different kind of secondary allergen be postulated, namely, that produced in every skin on physical irritation, then its existence would be disproved by the failure of the inversed transfer test; irradiation followed by the injection of serum containing reagins, as in the cases cited here, is not successful. The mutual action of the secondary allergen due to irradiation and of the reagin administered later should result in a wheal just as the meeting of the secondary allergen with the reagin administered previously. Thus the missing wheal on inversed transfer does not favor the assumption of a secondary allergen in these other cases.

TABLE IV

	READING AFTER	SITES OF THE SERUM: IRRADIATED	SITES OF THE SERUM: NONIRRADIATED
May 3.—(After 24 Hours) Irradiation With a Jesionek Lamp			
1. Test: 50 cm., 5 min.	10 min.	Flat wheal, itching	Larger wheal, itching
2. Test: 50 cm., 7 min.	10 min.	Hyperemia, edema, itching	Typical urticaria, itching
May 4.—(After 48 Hours) Irradiation With a Jesionek Lamp			
3. Test: 50 cm., 6 min.	10 min.	Wheal $\frac{8\text{-}10^*}{10\text{-}10}$ mm., itching	Wheal $\frac{10\text{-}16^*}{15\text{-}15}$ mm., itching
4. Test: 50 cm., 6 min.	10 min.	Hyperemia size 8-12 mm. with slight edema, itching	Great edema 10-15 mm., itching
5. Test: 50 cm., 6 min.	10 min.	7-8 mm., itching	8-10 mm., itching

*The number above the line denotes the diameter of the wheal; that below the line denotes the diameter of the hyperemic areola.

The recently increasing number of passive transfer tests reported in cases of physical allergy should (from the viewpoint of a unitary biologic mechanism) identify physical allergy with other allergies. Apart from a few exceptions, the new books evade the problem by either not covering physical allergy at all, or regarding it as a nonallergic pathergic reaction and considering only cases with successful transfer as true allergies.

The first extension of the Doerr-Coca antigen-antibody theory has taken place due to the discovery that the general clinical symptoms

and the local ones arising in the cells affected by the irritant allergen are due not to the allergen-reagin reaction itself but rather to nonspecific tissue substances (H-substances) participating also in the normal cell life and liberated by the allergen-reagin reaction.* This theory generally accepted today renders necessary the assumption of a linkage between allergen and reagin though in a loose and reversible form. But even such a loose linkage cannot be presumed in physical allergy wherefore the theory had to be modified in order to bring physical and chemical allergy into harmony from a uniform biologic aspect. The modification consisted in regarding the proteinlike reagin† as a catalysator put into activity by its adequate specific chemical or physical stimulus. Nothing can be objected to in this concept of the organic catalysators exerting a specific action within the cell. In accordance with this, the hypothesis applicable to all kinds of allergies may be summarized as follows.

The allergen-reagin reaction is a colloid chemical process in which two factors take part: (1) the allergen a most variable extrinsic or intrinsic chemical or physical agent (a physical stimulus may act from within, e.g., heat), (2) the specific antibody pre-existing in certain cells, i.e., in the shock tissue (reaginogen ?), acting as an organic catalysator and activated by the allergen as specific stimulus whereby a tissue substance present in the normal cell life is being produced. Under the influence of the reagin acting like a catalysator the nonspecific tissue substances (H-substances‡) produced at a higher speed and in an enhanced grade bring about the clinical manifestations of the allergen-reagin reaction: first, a local reaction (inflammation), second, a general one (hemoclastic crisis and shock symptoms). The process can be schematically represented by the partial processes ensuing in the direction of the arrows: allergic agent → reaginogen → reagin → amino acids originating from proteids → biamines (histamine, etc.) → allergic inflammation and general symptoms.

On repeated irritation by the allergen the reverse process, i.e., a gradual decrease of the inflammation, takes place because a specific antibody, acting as a catalysator as well, termed, in this case, *dereagin* by Lehner and Rajka induces the production of tissue substances having, in contrast with the H-substances, a diminishing effect on the inflammation (R-substances) (Török). Several similar substances are

*Even under normal conditions, processes decomposing the tissue are set in motion by inflammatory influences. An outstanding part is played here by oxidative ferments. In the course of the processes potent biamines are formed from proteids (histamine through histidine, etc.). The role of the ferments in the production of the tissue substances has been experimentally proved by Török, Rajka, Kenedy, and Schönberger (Med. Klin. 1935. No. 37).

†The antibodies are protein bodies like normal serum globulins. They display also much resemblance to them regarding their physical, chemical, and serologic properties (Haurowitz).

‡The term H-substance is a collective conception, not less than five tissue substances with a vasodilating effect being known: histamine, choline, acetylcholine, adenylic acid, Gaddum's P substance.

known: adrenalin, the vasoactive hormone of the posterior pituitary, tyramine (Barger, Dale, and Laidlaw), the vitamin P of Szentgyörgyi reducing capillary permeability.*

This theory yields an explanation also for the passive transfer of physical allergies: the transferred reagin has first to enter the cell where it can, under the influence of the homologous allergen, exert a catalysator effect similar to that in the allergic organism. On induction at a distance the allergen is carried to the area of passive sensitization by the blood stream; in this respect only heat and cold are considered. In the experiment with the inversed transfer the allergen must be bound to the cell or influence it prior to the administration of the serum containing reagin. Very likely in such instance only the thermic influences of all physical stimuli should be regarded. Yet it must be noted that neither an inversed transfer nor an induction at a distance are reported with physical allergies. Kritchevsky writes that he had in physical allergy also a successful inversed transfer with his method (transfer to a white rat) but the description of the cases and the transfer is missing.

The following groups belong to the physical allergies: (1) Certain kinds of endogenous itching, *urticaria factitia*, (2) *cold urticaria* (cold dermatitis), (3) *heat urticaria* and heat dermatitis, (4) *photogenous urticaria* and some dermatitides due to light (eczema *solare*, prurigo *aestivalis*). The grouping of these presumably physical processes as allergic takes place on the basis of criteria which are generally liable to prove the allergic nature of a process. These criteria are as follows.

(1) *Positive dermal test* with the specific irritant. The physical stimulus induces in an intensity which causes no inflammation in the normal person. There is an optimum for all stimuli, i.e., a certain degree of cold or a certain wave length of light, etc., which induce, when acting with an increased intensity, an inflammation in normal persons as well. The two degrees of inflammation do not always correspond to each other. Thus light, cold, and heat elicit urticaria in the allergic person and only a dermatitis like an erythema or eczema but no urticaria in the normal person. The difference between normal and allergic persons consists, as has been detailed above, in the fact that the allergic person harbors a specific enzyme which becomes active under the influence of a certain physical stimulus. This enzyme, called reagin, promotes, in the cells affected by the physical stimulus, the production of the tissue substances needed in raising an inflammation. Due to this, not only an agent considerably less than required normally for inflammation suffices to start the inflammatory process but also a different inflammative character occurs; i.e., the wheal with an acute serous exudation.

*This allergic theory was first explained before the 1938 session of the Hung. Dermatol. Soc. (Zentralbl. Hautkrkh. 63: 98, 1939). It has been published in detail (Börgy. Szemle 17: 113, 1939. Zentralbl. Hautkrkh., 64: 313, 1939).

As to the final result, it is irrelevant whether the reagin is constantly present on a constitutional basis or whether it is only temporarily produced in the shock tissues owing to some indigestion, liver disease, inflammatory foci, etc., or occasionally under the influence of photodynamic substances.

2. Application of the physical stimulus causes, especially when applied to a large skin surface, *general symptoms* and *hemoclastic crisis.* This phenomenon occurs, more or less, with the most physical allergies, its highest grade being found with the thermal allergy and the lowest one with the hypersensitiveness to light.

3. Specific *desensitization* can be effected. The suitable method has been worked out by Lehner and Rajka in which homologous physical irritants are applied with a gradually increasing intensity in connection with injections of autogenous blood. In physical allergy a thorough desensitization can be attained by this method so that the dermal tests or the hemocrisis can hardly, if at all, be elicited.

4. The greatest importance is ascribed to the *passive transfer* of the reagin, the carrier of specificity. No doubt the number of the successful transfers is few as compared with the negative experiments. Several factors may underlie the negative results. (1) Inadequate technique may be responsible. We would advise the use of several methods at the same time because the test may yield a positive result with one of the methods only, e.g., with the Lehner-Rajka or the Königstein-Urbach reaction while the PrKR may be negative (Fig. 2, Case 21). (2) At the time of the transfer experiment no transferable reagin circulating freely in the blood stream can be found. It is present also during these periods at the places of its production as it can be verified by the fact that the transfer can more frequently and with a greater intensity be achieved with the serum taken *after* the irritation. This fact has been proved in the cases of cold and heat urticaria by Lehner and Rajka, in light urticaria by Rajka, and further confirmation has been supplied in cold urticaria by Liebner, Weissenbach, Brisset, and Affolter.

Therefore a negative transfer test does not exclude the allergy beyond all doubt, and it is not allowable simply to list a negative result as a nonallergic pathergy or a positive one as allergy, but each case has to be judged on the basis of its general clinical and experimental appearance. Further, in a given case, partial proofs are to be accepted in the place of full proofs as one often accepts them in other kinds of allergy such as nutritive urticaria, asthma, migraine, etc., when partial shock is accepted in lieu of a full shock. Today a sufficient number of successful transfers can be brought up as evidences for the existence of physical allergy. First of all, the thermic allergy is referred to. The

most difficult task is to prove the existence of the reagins through passive transfer in a light allergy case. The successful transfers recorded refer with a single exception not to the light urticaria but to other photodermatoses (Fig. 2). Only Bernstein's case and the one presented here are successfully transferred cases of light urticaria. A positive PrKR has been obtained only in the latter, whereas in Bernstein's case the reagins could not be demonstrated except through animal experiments. The rarity of the successful transfers can, beside the rare occurrence of photoallergy, especially of the genuine light urticaria, hardly be explained merely by faulty technique. There is probably still another factor pointed to by the author of this paper and Lehner in connection with the transfer of hypersensitivity to trichophytin, tuberculin, and luetin that the transfer is only possible in a specially "strong" hypersensitivity, i.e., at a high reagin titer of the blood when the reagins fixed in the cells enter the circulation in an appreciable quantity.

Table III records positive passive transfer experiments with physical allergy.

The transfer of the photogenous urticaria has raised the question whether it is a genuine allergy in which really only reagins are transferred in the serum which enter the cells of the test person and become activated under the influence of the homologous light or only a *photodynamic phenomenon* occurring secondarily to the transfer of an already known photosensitizing substance becoming active likewise under the influence of light. The decision of the problem is by no means easy since the reagin is a specific catalysator possessing in our concept a "photosensitizing" effect in the cases of light urticaria. The theoretic difference between the two concepts consists in the fact that for the allergic theory it presumes a reagin put in action by the light and inducing urticaria through forming H-substances. In contradistinction to this, although no investigator could as yet show the presence of photodynamic substances (Fig. 1), it might be porphyrine or another photocatalysator, in cases of light urticaria. Most authors suppose that, in addition to the allergic pathogenesis, photosensitizing substances are also present.

The role of a photosensitizing substance in the light urticaria must be considered because it had been established by Duke, later Frei, Blum and Pace, that the irradiation of the intradermally injected hematoporphyrine yielded a wheal appearing with a special intensity subsequent to an irradiation corresponding to the absorption line. Duke observed the phenomenon in only one patient sensitive to light, whereas Frei obtained a positive reaction also in normal persons when the hematoporphyrine solution 1:1,000 was being irradiated from three to six hours after injection, or when the places where rose bengale had

been administered intradermally were exposed to a mild irradiation one or two days after injection. According to these, the injection of a photodynamic substance gives rise to an urticaria in the same manner as the transfer with the PrKR. However, the following *differences* have been observed.

1. Once the irradiation has taken place on the day of the injection a strikingly strong reaction occurs. Unlike this, no wheal arises with the PrKR at the second irradiation once the place was irradiated and the urticaria developed.

2. The optimum time for the reaction with hematoporphyrine lies between three and six hours. After twenty-four hours the irradiation is ineffectual in contrast to the passive transfer reaction after twenty-four or forty-eight or even seventy-two hours wherein no response can be obtained in the first hours subsequent to the injection, which time is needed for the reagins to become cell fast. Stein found the photosensitizing substance in a case of hydroa, a nonallergic photodermatosis, with positive porphyrinuria after three hours, in accordance with the optimum time of transfer with hematoporphyrine.

3. At the places where, after the injection of photodynamic substances, hematoporphyrine, rose bengale, and irradiation, a wheal has been elicited, frequently a late reaction arises after the wheal has developed into a congestive edematous inflammation. This late reaction also occurs when the photodynamic substance is administered intradermally or subcutaneously without a consecutive irradiation, e.g., as a therapeutic measure, and it heals after five to fourteen days nearly always with an obstinate pigmentation. A similar phenomenon has been observed by Epstein after the intradermal injection of sulfanilamide and its irradiation. In contradistinction to this, the area of the PrK transfer heals without a late reaction, without pigmentation or any other sign. The late inflammation with hematoporphyrine can be avoided by careful irradiation only resulting in a wheal. No such care is necessary with the PrKR; a late reaction does not ensue even after a very strong (five, six, or seven minutes) irradiation on the place of the injection, excepting an occasional diffuse light erythema within which the wheal cannot be detected on the next day. It is noteworthy that there are great differences between the adequate doses; Frei irradiates to obtain a hematoporphyrine wheal from 50 cm. for thirty minutes (Bach lamp). To have the same effect with the PrKR three to five minutes are sufficient.

4. The artificial hematoporphyrine urticaria likewise occurs whether it be irradiated with sunlight, mercury vapor lamp, Sollux, etc., with rays the UV or IR content of which have been absorbed by a thick windowpane or copper sulfate, respectively. No doubt, all of these light sources contain abundantly green rays which is of special concern regarding the absorption maximum of the hematoporphyrine and the rose bengale both

lying within the green spectrum.* In our case of light urticaria no wheal formation occurred either to green rays or following the irradiation with Sollux. This fact is not in keeping with the role of hematoporphyrine but it does not exclude its precedent form (porphyrinogen) or any other sensitizing substance. Blum and West thought of carotinoids in their case, as the patient was sensitive to the radiation between 4,500 and 4,900 A°. They could not, however, induce sensitivity through the injection of carotin or xantophyll.

5. The action of diluted solutions of rose bengale or hematoporphyrine is diminished or abolished by addition of serum. As a contrast, the PrKR is accomplished with serum. The ineffectiveness of the transfer experiment with urine is also an argument against porphyrine.

6. In allergic diseases reagins are found augmented in the circulation in the first half hour following the irritation (Lehner and Rajka). It may even occur that no free reagin is present in the blood prior to the irritation, only the latter giving rise to their entering the circulation (Table III). The same has been observed with our patient suffering from light urticaria. This observation again discourages the presumption of a photodynamic substance which hardly would increase in the organism during such a short time (twenty to thirty minutes). Carrié states that irradiation does not exercise a marked influence on the daily porphyrine output through the kidneys; nevertheless such an influence is possible, Hager having demonstrated the change of porphyrine output in hourly determinations. The change of the output (partly enhanced, partly reduced) was present in thirty or 66 per cent of the observations when blue or red light was being employed respectively.

7. Frei, Wucherpfennig, and other authors cite light urticaria among the phenomena of photosensitization, particularly because (1) strong photosensitizers are efficacious in very diluted solutions (rose bengal 1:2,000,000, hematoporphyrine, 1:500,000); (2) in these very dilute solutions the substances lose their effectiveness after preceding insolation just as the serum in the PrKR after preceding irradiation. In contradistinction to this, the light urticaria cannot be identified with a photodynamic sensitization in the view of Blum, Watrous, and West. These authors generally distinguish three types of light reactions: (a) normal erythema following UV radiation with a comparatively long latency and pigment formation. Both the erythema and pigment are independent of oxygen; (b) photogenous urticaria solaris as an early reaction to the visible rays between 4,000 and 5,000 A°. It is not followed by a late reaction or pigment formation and does not depend on the presence of oxygen; and (c) photodynamic early wheal reaction secondary to photosensitization. This photosensitization is generally

*The red hematoporphyrine mostly sensitizes to the complementary green about 5,000 A° (Arzt and Haussmann). Its absorption lines lie at (1) 6,160-6,180 (orange), (2) 5,650-5,680 (yellow), (3) 5,300-5,350 (green), (4) 4,970-5,010 (green). Those in the green and yellow area show the strongest absorption. Blum and Pace found beside the four lines in the visible spectrum also a very strong absorption at 3,800 A°.

due to a radiation absorbed by the photosensitizer. Like (b) it is an early reaction, but it is followed by pigment formation and bound to the presence of oxygen.

Neither does Bernstein believe that photosensitizer is transferred because, should it be so, then on irradiation of the patient also a late reaction would occur as an intensification of the proper light reaction. However, neither in the patients of Bernstein, Blum, Allington, and West nor in our case did a late reaction occur after adequate doses. Duke, Rowe, Epstein, and others too assume a photoallergic mechanism. In the light erythema case of Callaway he observed a considerable increase of coproporphyrine I, but he did not ascribe the light sensitivity to this substance. As mentioned above all of the cases of light urticaria gave a negative reaction for hematoporphyrine including that of Duke although it responded to the intradermal hematoporphyrine with a wheal (the patient of Urbach who sometimes was porphyrine positive was an exception). It should be noted that traces of coproporphyrine III, and probably of uroporphyrine III, might be found in the normal urine, depending on the constitution, the meat intake, etc. (the former amounts to 0 to 60 micrograms in twenty-four hours, being rather a constant quantity with about 10 per cent shift). In the serum there is no porphyrine; in the erythrocytes a slight quantity of protoporphyrine is present. In light dermatosis the augmentation of the porphyrine from 100 to 400 per cent frequently can be observed (Tropp).

SUMMARY

1. A case of urticaria *photogenica* can safely be assumed to be a true allergy corresponding to the theory of allergy and based on the allergen-reagin reaction.

2. The physical allergies are of a true allergic nature, especially thermal and mechanical allergy.

3. The resemblance of light urticaria to other allergies, from both the theoretical and experimental practical viewpoint, is demonstrated.

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STUDIES IN GUINEA PIG ANAPHYLAXIS WITH THE HOUSE DUST ANTIGEN

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THE nature and source of house dust antigen has been the subject of many investigations. Opinion as to the essential character of the antigen is principally divided into two opposite views. One supports the theory that a single definite antigen exists in all house dust, and the other supports the theory that dust is a combination of such antigens as are commonly found in the furnishings of the home; e.g., wool, goat hair, silk, cotton, and feathers.

Cooke, in 1922,[1] stated that house dust contains a specific active principle in addition to various other atopens. Frugoni and Ancona,[2] van Leeuwen,[3] and Cohen[4, 5] contended that the dust antigen develops in ageing feathers, in kapok, and in cotton linters of bedding and overstuffed furniture. Whether or not each of these sources produces the same or a distinctly different specific antigen has not been determined in any of these investigations.

Cohen's experiments were done with cotton linters taken from the previous season's crop. Extracts of the fresh cotton linters gave negative skin reactions in ten persons who were known to be dust-sensitive. An extract was then prepared from samples of cotton linters which had been allowed to age for several months. This extract gave positive skin reactions in those dust-sensitive persons who had failed to react to the fresh linters extract. Normal subjects failed to show any skin sensitivity to this extract. Passive transfer tests were not done. Cohen concluded that the active principle in house dust is a single specific antigen resulting from a degenerative product of cotton linters.

The work of Albert, Bowman, and Walzer,[6] on the other hand, tends to support the multiple component theory. These workers tested fifty-four atopic persons with a stock house dust extract prepared after the manner of Coca and Milford.[7] They obtained eight reactions of three or four plus intensity, twenty-four of two plus, and twenty-two of one plus. No completely negative skin reactions were obtained with their extract. Passive transfer tests were performed with the sera of all of these patients. In none of these sera did the skin-sensitizing antibody

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Read at the Sixth Semiannual Meeting of the Allergy Division of the Jewish Hospital, May 22, 1939; abstracted in J. ALLERGY **10**: 479, 1939. This article contains no reference to the papers on the same subject by Hampton, Stull, and Cooke, the first of which appeared almost simultaneously with this one.[17-20] These authors, like I, confirm the findings of Coulson and Stevens.[15] However, they are in disagreement with me in their conclusion that the Dale technique lends itself to the study of the nature of the dust antigen.

for house dust exist independently of the other inhalants. In each case in which a positive transfer to dust was obtained, a positive transfer to at least one other inhalant was also noted. Seventy-two additional sera in which the dust reagin was demonstrated invariably contained reagins for one or more of the other members of the inhalant group. Conversely, when no dust reagins were found, there were no reagins for the other common dust-producing inhalants.

The purpose of the present study was to determine whether by animal experiments any further information could be gained on the nature of the dust antigen. This first required the successful sensitization of guinea pigs with the house dust antigen. Attempts at such sensitization of the guinea pig had, until very recently, been uniformly unsuccessful. Ramsdell and Walzer[8] failed to produce sensitivity in the guinea pig with house dust, as did Wagner and Rackemann[9] with kapok dust. Cohen, Nelson, and Reinarz[10] did not succeed in attempts to sensitize rabbits to cotton linters. Van Leeuwen[11] employed a mold (*Aspergillus fumigatus*) which he believed was the active principle in house dust, but could not produce sensitivity to this antigen.

Harrison, in 1934,[12] presented his alum precipitation technique for the more effective sensitization of guinea pigs with ragweed pollen. Caulfeild[13] successfully duplicated Harrison's work in 1936. In the present study, Harrison's principle of alum precipitation of extracts was employed in the attempt to induce sensitivity in guinea pigs to house dust extract. This investigation had almost been completed when the report of Coulson and Stevens[15] appeared announcing successful sensitization of guinea pigs with alum-precipitated house dust extract. Their findings will be reviewed presently.

TECHNIQUE

The animals used throughout the experiment were female, virgin guinea pigs, weighing from 200 to 275 Gm.

Preparation of the Antigen.—The house dust extract was prepared according to the method of Coca and Milford.[7] A 10 per cent solution of potassium alum was then added to this extract to yield a final concentration of 1 per cent alum. Precipitates of varying intensities were obtained with different samples of dust extracts. After twenty-four hours, the alum-precipitated extract was thoroughly shaken and from 1.5 to 2.5 ml. were injected subcutaneously into guinea pigs for sensitization. House dust extract untreated with alum was used for the shocking injections.

The nonspecific effect of a single intravenous dose of the extract was tested by injecting from 1 to 2 ml. of dust extract intravenously into twenty normal, nonsensitive guinea pigs. Several of the animals which received doses of more than 1 ml. exhibited clonic contractions of the muscles of the back, neck, and extremities within two minutes after

the intravenous injection. These symptoms persisted for only a short time (one to four minutes) and were of an entirely different character than the usual anaphylactic symptoms. Uneventful recovery occurred in all animals.

SENSITIZING TECHNIQUE

Five series of animals were employed in the studies. They were injected subcutaneously with from 1.5 to 2.5 ml. of the alum-precipitated extracts of house dust. In series A, house dust No. 8, which was being employed for routine testing in the allergy clinic, was used. In the remaining experiments, a freshly prepared extract of house dust was employed. House dust No. 8 gave a copious precipitate with the alum, while the other extract which will be referred to as D extract, gave only a slight precipitate. No adjustments of the pH of the extracts were made.

DALE TECHNIQUE

From thirty to sixty days after the sensitizing injection, each animal was tested for sensitivity by means of the intravenous route; many were also tested by the Dale technique. In twenty-two of the guinea pigs the two-stage procedure of Walzer and Grove[14] was employed. This technique consists of testing two smooth muscle strips from each animal, one of these strips (A) having been removed before and the other (P) following the intravenous shocking injection of the specific antigen. An empty strip of jejunum or one uterine horn was rapidly but carefully removed from the sensitized guinea pig according to the technique advised by Walzer and Grove and was placed in the Dale bath, which was kept at a constant temperature of 37° C. and at a constant volume of 75 ml. The abdominal wound was quickly closed with skin clamps and the testing dose of house dust extract was then administered intravenously into the vein of the leg. Testing doses of the extract varied from .02 to 1 ml. After the general anaphylactic shock reaction occurred, the second uterine horn or a second jejunal strip was removed for comparative Dale tests with the specimens obtained prior to the intravenous testing. Those strips which reacted when the house dust extract was added to the bath were carefully washed and retested after an adequate rest period. This procedure was repeated until the strip failed to contract upon the addition of the house dust extract. Histamine in a 1:1000 dilution was always added at this point to test the viability of the strip.

RESULTS WITH INTRAVENOUS AND DALE TESTING

The first series (series A) consisted of nine guinea pigs. Testing was done by the intravenous and Dale techniques after a sensitizing period

varying from thirty to forty days (Table I). Eight of the nine animals which were given a 1 ml. intravenous dose of house dust extract died of anaphylactic shock in from two to twenty minutes. Post-mortem examination of the lungs showed definite emphysema in all eight animals. Those guinea pigs which were allowed a sensitizing period of forty days experienced a much more rapid anaphylactic death than those animals which had had shorter sensitizing periods. Positive Dale reactions were obtained in five of the seven strips tested. One strip gave a questionable reaction to both house dust extract and to histamine. The other strip failed to react to the house dust extract but did give a positive reaction (two plus) when histamine was added to the bath. These results gave evidence of the high degree of sensitivity which could be induced in guinea pigs by the subcutaneous injection of an alum-precipitated extract of house dust. However, a longer sensitizing period than is ordinarily necessary when more potent antigens are used seems to be required to produce a high degree of sensitivity with the house dust antigen.

TABLE I

RESULTS OF TESTS FOR HYPERSENSITIVENESS TO DUST IN SENSITIZED GUINEA PIGS

Series A

INTRAVENOUS TESTING						DALE TESTING		
GUINEA PIG NO.	SENSITIZING PERIOD IN DAYS	SENSITIZING DOSE (ML.)	SHOCKING DOSE (ML.)	RESULT	PULMONARY EMPHYSEMA	FIRST TEST WITH 1 ML.	SECOND TEST WITH 1 ML.	HISTAMINE 1:1000
162	30	1.5	1	x, 10 min.	+++	0	0	++
160	32	1.5	1	x, 10 min.	++	+++	0	++++
168	32	1.5	1	x, 12 min.	++	+++	0	+++
166	33	1.5	1	x, 20 min.	+++	++	++	+++
164	33	1.5	1	x, 12 min.	+++	+++	0	+++
158	34	1.5	1	Negative	0			
165	40	1.5	1	x, 3½ min.	++++			
163	40	1.5	1	x, 2 min.	++++	++	0	++
167	40	1.5	1	x, 4 min.	++++	±	0	±

X, Anaphylactic death.

To prove the specificity of the Dale reaction, an effort was made to determine if actual desensitization to house dust occurred after the intravenous injection of that antigen. For this purpose, Walzer and Groves' modification of the Dale technique was frequently employed in subsequent experiments.

In the second series of 11 guinea pigs (series B) the animals were sensitized with house dust extract D. A sensitizing period of from twenty-eight to forty-five days was allowed. Shocking by the intravenous route resulted in death in all eleven animals. The lungs were emphysematous in each case. In three instances the single-stage Dale technique was carried out and in six the two-stage technique. Table II shows the results of the intravenous and Dale testing. In this series,

five animals were tested intravenously with 1 ml. of the extract, two with 0.75 ml. and four with 0.5 ml. This variation of the shocking dose resulted in slight differences in the severity of the anaphylactic shock. Death occurred in from two and one-half to four minutes in the five animals shocked with 1 ml. and in two and one-half and three and one-half minutes, respectively, in the two shocked with 0.75 ml. However, the four animals into which only 0.5 ml. was injected died in three and one-half, six, twelve, and fourteen minutes, respectively. A summary of the two-stage Dale studies showed that of the nine A strips tested, eight gave positive reactions to the added antigen; of these eight strips, seven were apparently desensitized (to the same test dose) with the first addition of house dust; i.e., the strips failed to contract when, after a change of bath, they were retested. Only two of the six strips which had been removed from the animals after the intravenous shocking (P strips) reacted to the addition of house dust to the bath. One of these gave a slight but definite contraction and the other only a questionable contraction. This experiment, therefore, demonstrated that apparent desensitization both in vitro and in vivo could be effected with the dust antigen.

TABLE II

RESULTS OF TESTS FOR HYPERSENSITIVENESS TO DUST IN SENSITIZED GUINEA PIGS

Series B

INTRAVENOUS TESTING						DALE TESTING				
						RESULT WITH 1 ML.				
						STRIP A		STRIP P		
						TEST				
GUINEA PIG NO.	SENSITIZING PERIOD DAYS	SENSITIZING DOSE OF D EXTRACT (ML.)	SHOCKING DOSE OF D EXTRACT (ML.)	RESULT	PULMONARY EMPHYSEMA	1	2	1	2	HISTAMINE 1:1000
34	28	1.5	1.0	x, 2½ min.	+++					
29	29	1.5	0.5	x, 14 min.	++	++++	0	0		+++
20	30	1.5	0.5	x, 12 min.	+++	++++	0			++++
35	32	1.5	0.5	x, 3½ min.	++++	++++	0	+	0	+++
31	34	1.5	0.5	x, 6 min.	+++	++	++	0	0	++
18	35	1.5	1.0	x, 3½ min.	+++	++	0	0		++
22	37	1.5	0.75	x, 2½ min.	+++	+++	0	0	0	++
27	40	1.5	0.75	x, 3½ min.	+++	+++	0	±	0	++++
21	41	1.5	1.0	x, 3½ min.	++	0	0			++
30	45	1.5	1.0	x, 4 min.	++++	++++	0	0	0	++++
33	28	1.5	1.0	x, 3 min.	++++					

X, Anaphylactic death.
A, Strip taken before intravenous testing.
P, Strip taken after intravenous testing.

Series C, D, and E, comprising a total of thirty-one guinea pigs, gave comparable results with intravenous and Dale testing.

In series C, seven guinea pigs were shocked by the intravenous route. In three instances the two-stage Dale technique was employed (Table III). In series D (Table IV), an attempt was made to determine the smallest intravenous dose of the dust extract with which anaphylactic

TABLE III

RESULTS OF TESTS FOR HYPERSENSITIVENESS TO DUST IN SENSITIZED GUINEA PIGS

Series C

INTRAVENOUS TESTING						DALE TESTING				
						RESULT WITH 1 ML.				
						STRIP A		STRIP P		
						TEST				
GUINEA PIG NO.	SENSITIZING PERIOD IN DAYS	SENSITIZING DOSE OF D EXTRACT (ML.)	SHOCKING DOSE OF D EXTRACT (ML.)	RESULT	PULMONARY EMPHYSEMA	1	2	1	2	HISTAMINE 1:1000
192	47	2.5	0.25	x, 3½ min.	++++	++++	0	+	±	+++
194	37	2.5	0.75	x, 2½ min.	++++	+++	0	0		+++
182	40	2.5	0.25	x, 4 min.	++++	+++	0	0		+++
200	48	2.5	0.10	x, 8 min.	++++					
198	62	2.5	0.2	++						
191	62	2.5	0.5	x, 6 min.	+++					
196	63	2.5	0.5	x, 7 min.	++++					

X, Anaphylactic death.
A, Strip taken before intravenous testing.
P, Strip taken after intravenous testing.

TABLE IV

SUMMARY OF RESULTS OF TESTS FOR HYPERSENSITIVENESS TO DUST BY THE INTRAVENOUS AND TWO-STAGE DALE TECHNIQUES

Series D

INTRAVENOUS TESTING					DALE TESTING				
					RESULT WITH 1 ML.				
					STRIP A		STRIP P		
					TEST				
GUINEA PIG NO.	SENSITIZING PERIOD IN DAYS	SHOCKING DOSE (ML.)	ANAPHYLACTIC REACTION	PULMONARY EMPHYSEMA	1	2	1	2	HISTAMINE 1:1000
60	36	0.05	+++		+++	0	0		++++
61	40	0.25	0		+++	0	++	0	++++
56	43	1.00	x, 5 min.	+++	++++	0	0		+++
54	36	0.5	x, 7 min.	++++	+++	0	0		++++
63	41	0.25	+++		++	0	0		++++
65	44	0.4	x, 3 min.	++++	++++	0	0		++++
51	40	0.1	x, 10 min.	+++	+++	0	0		++++
64	47	0.25	+++		++	0	0		++++
57	48	0.05	+++				0		++++
55	48	0.10	x, 3½ min.	++++	++++	0			
62	48	0.05	x, 5 min.	++++		0			
59	48	0.05	x, 4 min.	+++		0			

X, Anaphylactic death.
Sensitizing dose of 2.5 ml. for all animals.

death could be produced. A 0.05 ml. dose of the extract employed was sufficient to produce death in two instances, and in two other animals, +++ anaphylactic reactions resulted from this dose. In a series of twelve guinea pigs (series F) tested with 0.02 ml., mild anaphylactic shock was noted in only two animals (Table VI). No deaths occurred

TABLE V

RESULTS OF TESTS FOR HYPERSENSITIVENESS TO DUST IN SENSITIZED GUINEA PIGS

Series E

GUINEA PIG NO.	SENSITIZING PERIOD IN DAYS	SENSITIZING DOSE OF D EXTRACT (ML.)	SHOCKING DOSE OF D EXTRACT (ML.)	RESULT	PULMONARY EMPHYSEMA	DALE TESTING: RESULT WITH 1 ML. STRIP A TEST 1	STRIP A TEST 2	STRIP P TEST 1	STRIP P TEST 2	DALE TESTING: HISTAMINE 1:1000
37	36	2.5	1.0	x, 3½ min.	+++	+++	0	0		++++
66	36	2.5	1.0	x, 4 min.	++++	+++	0	+	0	+++
45	37	2.5	1.0	x, 3½ min.	++++					
44	37	2.5	1.0	x, 2½ min.	++++	+++	0	0		+++
28	40	2.5	0.5	x, 4 min.	++++					
42	41	2.5	1.0	x, 4½ min.	++++					
46	41	2.5	0.5	x, 4 min.	++++					
58	43	2.5	0.5	x, 5 min.	++++					
26	43	2.5	0.5	x, 3 min.	+++					
36	44	2.5	0.25	x, 5 min.	+++					
53	44	2.5	0.5	x, 3½ min.	++++					
52	44	2.5	0.5	x, 6 min.	+++					

X, Anaphylactic death.
A, Strip taken before intravenous testing.
P, Strip taken after intravenous testing.

TABLE VI

SUMMARY OF RESULTS OF TESTING FOR ANAPHYLAXIS BY INTRAVENOUS ROUTE WITH 0.02 ML. OF ANTIGEN

Series F

GUINEA PIG NO.	SENSITIZATION PERIOD IN DAYS	SENSITIZING DOSE (ML.)	SHOCKING DOSE (ML.)	ANAPHYLACTIC DEATH	GENERAL ANAPHYLACTIC SYMPTOMS
248	35	2.5	0.02	0	0
260	35	2.5	0.02	0	0
246	36	2.5	0.02	0	++
252	36	2.5	0.02	0	0
253	37	2.5	0.02	0	0
251	37	2.5	0.02	0	0
256	37	2.5	0.02	0	0
249	37	2.5	0.02	0	0
254	40	2.5	0.02	0	+
255	40	2.5	0.02	0	0
257	40	2.5	0.02	0	0
247	40	2.5	0.02	0	0

+, Scratching of nose and slightly ruffled fur.
++, The above symptoms plus slight cough.

with this shocking dose. These experiments demonstrated that although intravenous shocking doses of as little as 0.05 ml. could cause anaphylactic death, only intravenous shocking doses of 0.4 ml. or more were able to cause fatal reactions with any degree of regularity.

Experiments were then undertaken to determine the greatest amount of dust that could be administered intravenously without producing nonspecific reactions. As previously noted, it was found that doses of *more* than 1 ml., when introduced into normal guinea pigs, frequently resulted in anaphylactoid symptoms.

Similar studies with the Dale technique revealed that 0.5 ml. was the smallest amount of house dust which, when added to the bath, produced a positive reaction with regularity. Only one of ten sensitive strips tested reacted to 0.05 ml. Tests on normal strips showed that doses of more than 1 ml. frequently caused nonspecific contractions.

Summarizing the results of testing by the Dale technique in series A, B, C, D, and E, it was found that strips removed before intravenous shocking (A strips) gave positive reactions in twenty-nine of thirty-one tested (Table VII). Those removed after shocking (P strips) failed in seventeen of twenty-two tested to contract upon the addition of house dust to the bath. Of the twenty-nine A strips that gave positive results when tested in the Dale bath, only two responded to a second stimulation with the same dose. None responded to a third exposure.

TABLE VII

SUMMARY OF RESULTS OF SINGLE AND TWO-STAGE DALE TESTING

SERIES	NUMBER OF ANIMALS	NUMBER TESTED BY DALE TECHNIQUE	NUMBER OF POSITIVE REACTIONS WITH A STRIPS ON FIRST TESTING	NUMBER OF POSITIVE REACTIONS WITH A STRIPS ON SECOND TESTING	NUMBER OF P STRIPS TESTED	NUMBER OF POSITIVE REACTIONS WITH P STRIPS ON FIRST TESTING	NUMBER OF POSITIVE REACTIONS WITH P STRIPS ON SECOND TESTING	IN VIVO DESENSITIZATION	IN VITRO DESENSITIZATION
A	9	7	6	1	0	0		0	0
B	11	9	8	1	7	2○△	0	5	2
C	7	3	3	0	3	1△	1○	1	2
D	12	9	9	0	9	1	0	8	1
E	12	3	3	0	3	1△	0	2	1

○, ± reaction.
△, Weak positive (+) reaction.

Of the five P strips that reacted positively, one gave a ++ reaction, three responded with weak (+) contractions, and in one the result was borderline (±). In one of the five, a borderline reaction was obtained on restimulation of the strip with a second dose of the antigen. Fig. 1 illustrates the contractions obtained with the two-stage technique in one (Guinea Pig 61) of the five animals in which there had been incomplete in vivo desensitization as a result of gross anaphylactic shock. The final apparent desensitization in the Dale bath is demonstrated. Fig. 2

illustrates an instance (Guinea Pig 56) of complete in vivo desensitization after gross anaphylactic shock.

All of the above experiments demonstrate the specificity of the contractions obtained with the Dale technique in animals sensitized with the dust antigen, when the testing doses were within the range indicated.

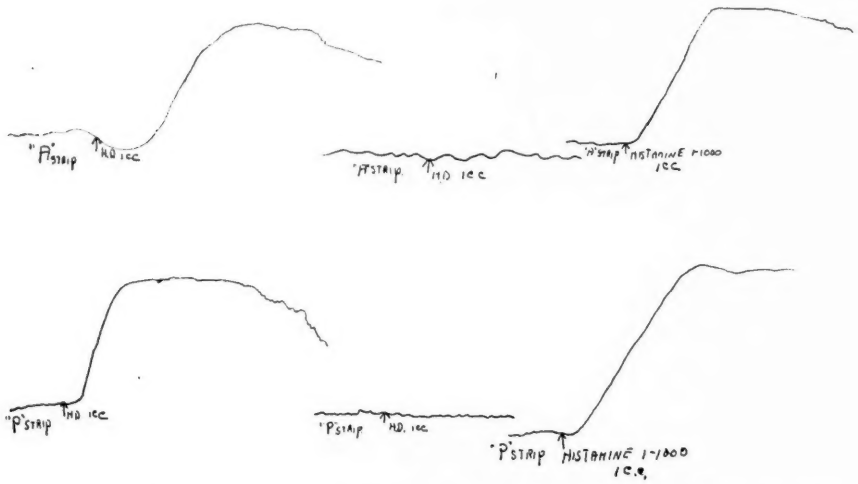

Fig. 1 (G. P. 61).—Graphs showing incomplete desensitization in vivo by intravenous anaphylactic shock and apparent completion of desensitization in the Dale bath. "A" strip removed before intravenous shocking; "P" strip removed after intravenous shocking; bath changed between additions of antigen.

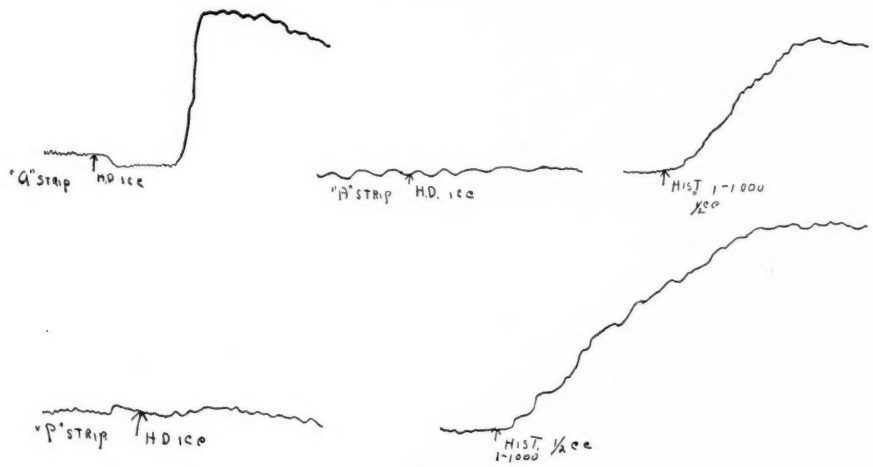

Fig. 2 (G. P. 56).—Graphs showing positive reaction in "A" strip and apparent desensitization of "P" strip by intravenous shock. "A" strip removed before intravenous shocking; "P" strip removed after intravenous shocking; bath changed between additions of antigen.

DISCUSSION

In March, 1939, Coulson and Stevens[15] reported successful sensitization of guinea pigs to house dust and cotton linters by use of alum-

precipitated extracts. They obtained fatal results when using from 0.4 to 0.8 ml. of their extract. Frequent anaphylactoid reactions were observed in nonsensitized pigs when 2 ml. of their dust were given intravenously. They state that "recognition of an inherent toxic principle in house dust extract rests upon differences in doses required to induce ante- and post-mortem evidence of anaphylactic death in sensitized guinea pigs and anaphylactoid symptoms in the unsensitized guinea pig."

In my experiments, anaphylactic death was occasionally observed with as little as 0.05 ml. of the house dust. However, to effect regularly fatal anaphylaxis, an intravenous dose of 0.4 ml. was needed. Anaphylactoid symptoms were frequently noted when more than 1 ml. of dust was given intravenously to normal animals. Doses of 0.5 ml. were required to produce contractions of sensitive strips in the Dale bath with regularity. However, the addition of more than 1 ml. of dust to the bath frequently caused nonspecific contractions in normal strips. These results confirm those of Coulson and Stevens, indicating that the range between doses which will give specific and nonspecific reactions is not a broad one, even when the animals are sensitized with the alum-precipitated antigen. The same limitations in working range pertain to the shocking dose in the Dale bath.

This technical difficulty has thus far blocked all of my attempts to study the basic nature of the dust antigen by means of gross anaphylactic and Dale techniques, for Coca and Kosockai[16] have demonstrated that sensitized animals, which appear to be completely desensitized when retested intravenously with the same shocking doses, may exhibit additional anaphylactic reactions when more concentrated (ten or more times) test doses of antigen are employed. Walzer and Grove[14] in their studies with egg white found that the same law of multiple proportions could be applied in eliciting repeated specific contractions of sensitized muscle strips with the Dale technique. Hence it is inadvisable to assume that *complete* desensitization to a particular antigen has been effected in anaphylactic hypersensitiveness until retests have been made with shocking doses from 10 to 100 times as great as the first.

My attempts to apply these critical principles to the study of the dust antigen in an effort to analyze its antigenic components by successive desensitization with different antigens were defeated by the peculiar nature of the dust antigen. Its working range as far as shocking dose is concerned was extremely limited (0.4 to 1 ml. for intravenous testing and from 0.5 to 1 ml. for Dale testing). Any attempt to increase the size of the test dose above 1 ml. tended to elicit nonspecific reactions with either technique. Furthermore, because dust is a relatively weak antigen, it had to be employed in undiluted form for sensitization and for testing. The same difficulties were encountered with feathers, goat

hair, wool, and other allergens which must be employed in studying the possible components of the dust antigen. No successful method has yet been found for further concentration of such extracts without rendering them too irritating for use in anaphylactic experiments.

SUMMARY

1. Guinea pigs can be sensitized with house dust by the use of alum-precipitated extracts.

2. The specificity of the reactions is convincingly demonstrated by the Dale studies.

3. Neutralization of sensitivity can be demonstrated with this technique, and the two-stage method demonstrated specific desensitization in vivo, and in vitro as well.

4. Because of the narrow working range of the dust excitant in anaphylactic techniques, these procedures do not lend themselves to conclusive studies of the antigenic nature of the dust excitant.

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THE PRESENCE OF INGESTED COTTONSEED PROTEIN IN WOMAN'S MILK

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DONNALLY[1] in 1930 studied the problem of the presence of ingested protein in woman's milk. He demonstrated by a passive transfer technique that the concentrated whey of breast milk, after raw egg was taken orally, contained demonstrable amounts of egg. He estimated by comparative tests with solutions of egg white of known potency that the concentration of egg white in these wheys ranged from one part in a million to one part in a billion. These findings have been challenged by subsequent workers.

Smyth and Bain,[2] in 1931, passively sensitized mothers and infants with intracutaneous injections of human serum containing reagins for egg. The mothers were given an egg meal, and their breast milk was then fed to the infants. Reactions occurred at the sensitized cutaneous sites of the mothers but not at the sensitized sites of the infants. This was offered as evidence that the breast milk did not contain the egg protein which was ingested by the mother.

Sterling and Fishman,[5] in 1938, reported symptoms of sneezing and of wheezing respirations in the breast-fed infant of a mother who was receiving injections of ragweed pollen extract. The symptoms regressed when the dosage of pollen antigen was decreased. It was concluded that the pollen extract injected into the mother was probably transmitted through the breast milk to the child.

Chemical studies by Adair,[3] Tyson,[4] and their co-workers have shown that following oral administration, sulfanilamide, bromides, and barbiturates are present in mother's milk.

The present study was undertaken in order to determine whether the results with egg obtained by Donnally could be duplicated with cottonseed protein.

The serum used in these experiments was taken from an individual highly sensitive to cottonseed. The blood was taken under sterile precautions and allowed to clot. The serum was removed, passed through a Seitz filter, and placed in tubes without preservative in the refrigerator. When the serum was titrated by the technique of Coca and Grove[8] with cottonseed antigen in a dilution of 0.01 mg. N per milliliter, positive passive transfer reactions were obtained in serum dilutions up to 1:1,024.

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Read at the annual meeting of the Society for the Study of Asthma and Allied Conditions, Atlantic City, May 3, 1941.

With undiluted serum, a reaction could be obtained on a passively sensitized site with cottonseed extract containing as little as 0.0000001 mg. N per milliliter.

Nonatopic mothers in the obstetric ward of the hospital were tested intracutaneously with cottonseed extract containing 0.10 mg. N per milliliter in order to rule out the presence of cottonseed sensitivity.

Twenty-four mothers, from 20 to 39 years of age, including four primiparas and twenty multiparas, were selected for study. Among these were five colored patients.

The mothers were put on a diet free from peas, beans, nuts, seeds, and fish; foods to which the patient supplying the serum was sensitive. A cutaneous site on the arm of each subject was passively sensitized with 0.05 ml. of the cottonseed serum. From forty-eight to seventy-two hours were allowed to elapse after sensitization before the antigen was given. On the day of the experiment the babies were put on formula feedings. The mothers were given no breakfast. Both breasts were pumped dry, and the specimens of milk obtained were used as controls.

Following the technique employed in previous studies,[6, 7] the mothers were fed a cottonseed meal consisting of from 5 to 20 Gm. of dehulled cottonseed ground to a fine powder and mixed with 30 ml. of water. In five cases the meal contained five Gm. of cottonseed, and in sixteen cases, 10 Gm. Twenty grams were fed to three women, but the meal was divided into two 10-Gm. doses, which were given one-half hour apart.

The cutaneous reactions which developed at the passively sensitized sites marked the absorption of cottonseed protein into the blood. They appeared in from three to forty minutes after the ingestion of the cottonseed meal. As noted in the protocol, the cutaneous reactions which developed at the sensitized sites varied from a slight erythema to a large wheal with surrounding erythema.

After the appearance of the cutaneous reaction, the breasts were pumped at various intervals. In thirteen cases, samples of milk were taken during the period of the cutaneous reaction. In these cases the breasts were pumped at intervals of from fifteen minutes to one hour for a period varying from one-half to three hours. In five cases, the breasts were pumped after five hours, in two cases, after twelve hours, and in four cases, after twenty-four hours. In Cases 9, 11, and 24, specimens of milk were taken even when no cutaneous reaction appeared at the sensitized sites following the cottonseed meal. The amount of breast milk obtained from the mothers varied from 23 to 195 ml.

Specimens of breast milk were then prepared for passive transfer studies. In preliminary experiments the concentration of milk by fanning had rendered it unsatisfactory for passive transfer studies so that this technique was abandoned. The samples of milk were centrifuged in order to remove the fat and were then passed through a Seitz filter. The filtrates were stored in the refrigerator.

The subjects used for passive transfer studies were normal nonatopic individuals in whom negative reactions were obtained to intracutaneous tests with cottonseed extract in a dilution of 0.1 mg. N per milliliter. During the course of the study, these individuals were also put on a diet excluding peas, beans, nuts, seeds, and fish. For the sensitization of a cutaneous site, 0.05 ml. of the undiluted cottonseed serum was used. Several sites were prepared on each subject. These were tested intracutaneously from three to seven days after sensitization. Comparative tests were made on the sensitized areas with the control mother's milk which was obtained just before the ingestion of the cottonseed meal and with the milk taken at various periods after the antigen was fed. Control tests with all breast-milk specimens were also made on unsensitized cutaneous areas.

TABLE I

RESULTS OF MILK TESTS ON PASSIVELY SENSITIZED SITES IN CASE 12

	CONTROL MILK		COTTONSEED MILK		NUMERICAL DIFFERENCE BETWEEN CONTROL AND COTTONSEED MILKS	RESULT OF TRANSFER TEST
	REACTION AT SENSITIZED SITE	REACTION AT UNSENSITIZED SITE	REACTION AT SENSITIZED SITE	REACTION AT UNSENSITIZED SITE		
Wheal Erythema*	Negative to slight 0+	Negative to slight 0+	Moderate +++	Negative to slight 0±		
Numerical evaluation	5 − 5 = 0		20 − 5 = 15		15 − 0 = 15	Strong positive

*Erythemas were recorded but not used in the numerical evaluation of the reactions which were made by comparing wheal reactions on the sensitized and unsensitized sites.

Numerical equivalents of reactions: Negative, 0; negative to slight, 5; slight, 10; slight to moderate, 15; moderate, 20; 1-4, doubtful positive transfer; 5-9, slight positive transfer; 10-19, strong positive transfer.

All milk specimens were tested on two or three subjects. Reactions were read in twenty minutes. Wheals were graded as negative, slight, moderate, or marked, according to their size. Erythemas were graded as 0, +, ++, +++, according to their size and intensity.

The method of recording and evaluating the results of the tests at the passively sensitized sites is illustrated by the findings obtained in Case 12 (Table I). With the control milk collected before the cottonseed meal, the reaction at the sensitized site was a negative to slight wheal with a zero plus (0+) erythema. A similar reaction was obtained with this milk when tested at an unsensitized site. The cottonseed milk specimen obtained from this mother produced a moderate wheal and a three plus (+++) erythema at the sensitized site. At the control or unsensitized area, a negative to slight wheal and a zero plus-minus (0±) erythema was noted.

In order to be able to average and compare the results of the tests on different cases, numerical equivalents were given to the wheal com-

ponents of the cutaneous reactions. A negative reaction was given a value of zero (0). Negative to slight, slight, slight to moderate, and moderate wheal reactions were given numerical values of 5, 10, 15, and 20. Substituting the numerical equivalents for the reactions obtained at the sensitized and unsensitized sites with the control specimen of milk of Case 12, a numerical value of zero (0) was obtained, representing the difference in value between the reactions at both sites. Numerical values of 20 and 5, respectively, were given to the moderate and negative to slight wheal reactions obtained with the cottonseed milk at the sensitized and control sites. The difference between these reactions was 15, which represented the numerical equivalent for the cottonseed milk reaction in this case.

TABLE II

SUMMARY OF RESULTS IN TWENTY-FOUR CASES TESTED FOR PASSAGE OF INGESTED COTTONSEED INTO BREAST MILK

CASE NO.	AGE	RACE	PRIMIPARA OR MULTIPARA	INGESTED COTTONSEED MEAL (GM.)	REACTION AT MATERNAL SENSITIZED SITE		TIME OF MILK COLLECTION	RESULT OF TRANSFER TESTS
					REACTION TIME (MIN.)	DEGREE OF REACTION		
1	25	W	Multipara	5	10	Positive	At 24 hr.	Negative
2	25	C	Multipara	5	10	Positive	At 24 hr.	Negative
3	26	W	Multipara	5	7	Marked	At 24 hr.	Slight Positive
4	22	C	Multipara	5	25	Erythema	At 24 hr.	Negative
5	34	W	Multipara	5		Erythema	At 12 hr.	Slight Positive
6	38	W	Multipara	10	6	Marked	At 12 hr.	Doubtful Positive
7	30	W	Multipara	10	4	Marked	At 5 hr.	Negative
8	38	W	Multipara	10	9	Marked	At 5 hr.	Doubtful Positive
9	21	C	Primipara	10		Negative	At 5 hr.	Slight Positive
10	34	W	Multipara	10	30	Slight	At 5 hr.	Doubtful Positive
11	28	W	Multipara	10		Negative	At 5 hr.	Negative
12	28	W	Multipara	10	5	Marked	For 3 hr.	Strong Positive
13	31	W	Multipara	10	15	Moderate to marked	For 3 hr.	Slight Positive
14	39	W	Multipara	10	35	Moderate	For 1½ hr.	Doubtful Positive
15	25	W	Multipara	10	10	Marked	For 1½ hr.	Negative
16	30	W	Multipara	10	3	Marked–	For 2 hr.	Negative
17	30	W	Primipara	10	8	Marked++	For 1½ hr.	Negative
18	30	W	Multipara	10	28	Marked	For 2 hr.	Negative
19	27	W	Multipara	10	6	Positive	For 3 hr.	Negative
20	38	W	Multipara	10	10	Positive	For 3 hr.	Negative
21	32	W	Multipara	10	10	Marked+	For 2½ hr.	Slight Positive
22	20	C	Primipara	20	40	Marked	For 2 hr.	Negative
23	26	C	Multipara	20	40	Positive	For 3 hr.	Slight Positive
24	24	W	Primipara	20		Negative	For 3 hr.	Doubtful Positive

The numerical equivalents obtained on testing two or more substitutes with each milk specimen were averaged in each case, and the results in the entire series of cases were recorded in Table II. A numerical equivalent from 1 to 4 was recorded as indicating a doubtful transfer. A value between 5 and 9 was considered a slightly positive transfer. A value between 10 and 19 was considered a strong positive transfer.

In only one case (Case 12) was a strong passive transfer reaction elicited with the mother's milk, indicating a high cottonseed content. In five cases doubtful results were obtained, and in twelve cases negative findings resulted.

TABLE III

PRESENCE OF ANTIGEN IN MOTHER'S MILK AT VARIOUS INTERVALS AFTER COTTONSEED INGESTION

NUMBER OF GRAMS FED								
20			0		±			
					+			
10		0	0	+	0	0	±	
		0	0		0	0		
		+			+	±		
					++	±		
						+		
5							+	0
								0
								0
								+
Interval between cottonseed meal and breast pumping (hr.)		1½	2	2½	3	5	12	24

0, no transfer; ±, doubtful transfer; +, slight positive transfer; ++, strong positive transfer.

In Table III the results obtained in the twenty-four mothers were tabulated according to the amount of cottonseed meal which was taken and the time at which the milk specimens were collected following the meal. In the six cases from whom samples of milk were obtained from one and one-half to two hours after a meal of 10 or 20 Gm. of cottonseed, the transfers were negative in five instances (83 per cent) and doubtfully positive in one (17 per cent). In twelve cases from whom samples of milk were obtained from two and one-half to five hours after cottonseed meals of 10 or 20 Gm., results were positive in five (42 per cent), doubtful in three (25 per cent), and negative in four (33 per cent). In five cases from whom specimens of milk were obtained from twelve to twenty-four hours after a meal consisting of only 5 Gm. of cottonseed, two positive (40 per cent) and three negative (60 per cent) results were obtained. In one case milk taken after twelve hours from a mother to whom 10 Gm. of cottonseed had been given showed a doubtful positive. In Cases 9, 11, and 24, in whom no positive reactions were obtained on the maternal sensitized cutaneous sites follow-

ing the cottonseed meal, the transfer tests are of particular interest. Cases 9 and 11 received 10 Gm. of cottonseed meal, and their milk samples were taken after five hours. A slight positive transfer test for cottonseed was obtained with the milk of Case 9 and a negative transfer with that of Case 11. In Case 24, milk samples were taken for three hours after a meal of 20 Gm. of cottonseed. The transfer in this case was doubtful. These results indicate that in these three cases the cottonseed in the maternal blood stream never reached a sufficient concentration to light up the sensitized sites. Enough cottonseed accumulated in the milk however to permit its detection by passive transfer technique in at least one of these cases (Case 9).

SUMMARY

1. By means of the passive transfer technique the presence of cottonseed antigen was definitely demonstrated in the breast milk of seven mothers of the twenty-four studied. In five the results were doubtful, in twelve they were negative.

2. Milk specimens taken in six cases during the first two hours after the ingestion of the cottonseed meal contained little or no antigen.

3. Milk specimens obtained in eighteen cases from two and one-half to twenty-four hours after the test meal gave definitely positive results in seven (39 per cent) and doubtful results in four cases (22 per cent).

4. Donnally's findings that egg white ingested by the nursing mother can be demonstrated in her milk by means of the passive transfer technique have been duplicated with cottonseed.

We are indebted to Dr. George Kornfeld, Attending Obstetrician, and to the members of his staff for extending the facilities of the Obstetrical Service for this investigation.

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DISCUSSION

DR. HARRY H. DONNALLY, Washington, D. C.—Of course, it is very gratifying to me to have Dr. Brunner confirm, in all of its essential details, the article published by me eleven years ago. A short time after my publication, György of Heidelberg, later of Cleveland, Ohio, demonstrated in the same manner the antigen in breast milk. György devised the same proof independently. The mothers in my series were kept on a diet free of egg and egg-containing foods for twenty-four to forty-eight hours. In my work the breast pump was applied at the peak of the anti-egg serum reaction in the skin of the mother's arm, and both breasts were pumped dry. Dr. Brunner has improved on this by showing that

the antigen could be demonstrated in the breast milk at varying periods, even as late as twenty-four hours after the ingestion of the antigen. This increases the importance of the demonstration because more antigen was shown in this way to go through the milk. He showed a more continuous secretion of the antigen in the breast milk. He demonstrated the presence of the antigen in a somewhat higher percentage of breast milks than I did, 40 to 60 per cent, whereas I demonstrated it in three of eight mothers, 37.5 per cent. Some of the egg white in solution in the breast milk was probably lost during the Seitz filtration.

Dr. Francis Scott Smyth, formerly of Washington University, now of the University of California, has on several occasions questioned my results. Dr. Brunner referred to his work in feeding breast milk obtained after the ingestion of eggs and while the anti-egg passive transfer site was reacting in the mother's arm. The anti-egg serum sites in the infant's arm did not react when the infant was fed this milk. The antigen may have been present in the breast milk but not in sufficient concentration to make a skin site react.

Finally, it was a very crude demonstration that I made to estimate the amount of egg white in breast milk by comparing the skin reaction in passive transfer sites to known dilutions of egg in salt solution or breast milk whey.

The significance of the cottonseed-protein reaction has been studied by Dr. Spiers and Dr. Stevens. They assert that the antigen of the cottonseed embryo does not occur in refined cottonseed oil. In contrast to this assertion, it is a common observation, even referred to by the President in his address today, that the ingestion of a refined cottonseed oil may occasionally cause symptoms, but not always. I have a young patient who is very sensitive to cottonseed as an inhalant and who usually can ingest cottonseed products with impunity.

McGrath in Walsh's clinic has demonstrated the antigen of the cottonseed in refined as well as in crude cottonseed oil.

Dr. Matthew Walzer, Brooklyn.—I believe that this paper is important not only because it confirms Dr. Donnally's work which seemed to be questioned in some sources, but also because it sheds considerable light on another very much discussed problem. Now, if cottonseed antigen, egg antigen, and other antigens appear in the mother's breast milk, we must assume that with the start of breast feeding infants are exposed immediately to all of the antigens which are consumed by the mother. In view of the fact that we know that reagins can be produced artificially within a period of two or three weeks, it is not unreasonable to assume that in certain predisposed infants sensitization can start at birth or within a day or two after birth and that reagins or other antibodies may appear in the blood stream within a month. Therefore, any evidence that previously has been submitted showing that sensitization must occur in utero because it appears so early in the infant must be reweighed on the basis of the information which we have heard here today. In other words, we must be careful in coming to the conclusion that, because the sensitivity appears so early, it is the result of sensitization in utero.

Dr. Harry S. Bernton, Washington, D. C.—I should like to ask if Dr. Brunner used the breast milk on sensitized animals and compared it with cottonseed preparations.

DR. WAGNER.—In this connection I should like to call attention to the cottonseed protein and linseed protein in cow's milk in almost all dairy cows, even those feeding outside in the summertime. Feed is augmented with cottonseed cake and linseed meal. We believe that patients get appreciable amounts of cottonseed and linseed by drinking dairy milk. Therefore, we feel that dairy milk should be eliminated from their diet when patients are found to be sensitive to cottonseed or linseed protein.

DR. HUBER.—I might say that I had one such patient who could not take milk unless the milk came from the farm where no oil cake was used.

DR. T. D. CUNNINGHAM, Denver.—I should like to cite a case which is rather interesting. A mother I was treating for hay fever had a nursing baby. The baby immediately developed eczema with each injection of hay fever extract. We stopped the hay fever injections, and it cleared up. We started them again, and it recurred.

DR. HARRY S. BERNTON.—I should like to say a word on behalf of cottonseed oil. We did not specifically state that cases of sensitiveness to cottonseed oil do not exist. We simply stated that in our experience we have taken patients who have reacted to cottonseed protein in a diluted form and have found in our group none who were sensitive to cottonseed oil.

DR. BRUNNER.—None of our experiments with milk were performed on animals because we were interested only in demonstrating cottonseed in milk.

THE PRODUCTION OF NONETIOLOGICAL SKIN HYPERSENSITIVITY TO FOODS BY NATURAL MEANS IN ATOPIC PERSONS

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IT HAS been clear for a long time to most of those who deal with atopic dermatitis, particularly after the age of infancy, that many positive skin tests to foods, especially if obtained by the intracutaneous method, are of no clinical significance whatever. Removal of the food does no good, and eating it does no harm. The older the patient, the more likely is this to be true.

Inasmuch as the skin is sensitized, there is reason to believe that, if the allergen in question reached it, dermatitis or urticaria would follow. Therefore either the ingested allergen is not being absorbed or some immune mechanism has been developed which prevents its union with the sensitized cells in the skin. It seems likely that both of these factors are operative. It is well known that lactalbumin, which is often absorbed unchanged in infancy, is not so commonly absorbed in childhood or in adult life; the same holds true for wheat protein and probably for many others. If there is no absorption, there can be no dermatitis, no matter how strongly the skin is sensitized or how much of the food is eaten. Egg white, on the other hand, is readily absorbed at all ages, and it is therefore possible that those patients who have positive skin tests to egg but no dermatitis or urticaria when they eat it have developed some mechanism which deals with the egg after it has been absorbed. That no such mechanism exists in normal persons with negative skin tests to egg is shown by the ease with which wheals can be produced on an artificially sensitized site in such a patient after he eats an egg.

It is not difficult to explain why an asthmatic patient or a patient with vasomotor rhinitis or gastrointestinal allergy with a positive skin test to any allergen may not have symptoms of asthma, rhinitis, or abdominal pain when he is exposed to the allergen. It may be said that, although the skin is sensitized, the appropriate shock tissue is not. When one considers the production of dermatitis, however, the situation is somewhat more complicated, for the appropriate shock tissue is apparently sensitized. However, a patient with respiratory allergy but no dermatitis will get no dermatitis from the injection and, therefore, certain absorption of his allergen, be the dose large or small, in spite of a large

From the Eczema Clinic, Children's Hospital, Boston, and the Department of Pediatrics, Harvard Medical School.

positive skin test to that allergen. If the dose is large, urticaria will occur, to be sure, but no dermatitis. On the other hand, if a patient already has dermatitis, he is likely to be made worse and new dermatitis is likely to develop, following the injection of any but the smallest doses of his allergen. Inasmuch as both types of patients develop urticaria from large doses, and as both have positive skin tests of the urticarial type, it is certain that in both there is sensitization of the vascular loops in the papillary layer of the skin. It is plain, however, that something more is necessary in order that dermatitis may be produced. There is surely some difference in the immunologic situation in the skin in uncomplicated hay fever and in atopic dermatitis, although they may both give identical wheal reactions to external tests. I believe there is at present no really adequate evidence to indicate what this difference is.

The difficulty of determining which skin tests to foods are etiological and which are not is one of the most annoying problems of atopic dermatitis. There seems to be no doubt, however, that after the age of infancy the latter group is the larger, and I wish to report briefly a few simple observations to illustrate the development of entirely nonetiological, naturally produced skin tests to a food in atopic persons.

In the last ten years, I have fed a milk-free food made of soybeans to many eczematous infants who had positive scratch or intracutaneous tests to milk protein. In some of these patients the positive milk test is etiological, and the dermatitis is cured by removing milk from the diet.

In others, removal of milk does no good and drinking milk does no harm. Inasmuch as the original milk sensitization was produced presumably by the daily ingestion of milk, the question arises whether the daily administration of soybean likewise produces sensitization. If any infants do become sensitized to soybean and still are cured of their eczema, why should they have eczema while taking milk and little or none while taking soybean?

Thirteen eczematous infants with positive scratch or intracutaneous tests to milk, all of which were etiological, so that the eczema was either greatly improved or cured when milk was removed from the diet and soybean substituted, were tested intracutaneously with soybean protein the day the soybean food was started. All were negative. They were then retested at one- or two-week intervals. Seven developed positive tests—one at the second week, two at the third, and four at the fourth week. There was no aggravation or return of dermatitis coincident with the development of the positive skin tests or at any time while the soybean food was being taken, in most cases over a period of months. Some of these patients were again fed milk after a few weeks, and the dermatitis immediately recurred. The soybean food was again resumed, and the dermatitis disappeared.

It is well known that the injection of very small amounts of protein may produce skin hypersensitivity. In order to be sure that the positive

soybean reactions were in reality produced by ingestion of the food, and not by the soybean protein injected at the first or second skin test, another series of fifteen eczematous infants who had never eaten soybean were tested with approximately the same number of tests and at the same intervals as those of the first group. All tests were negative. In still another group of twelve, no soybean tests were done at the start of soybean feeding. Tests were done from two weeks to eight months afterward and were positive in eight of the twelve.

Here, then, is a group of atopic persons with clinical symptoms of dermatitis due to absorption of milk protein. The dermatitis is relieved by removal of milk protein. They ingest each day large amounts of a different protein in exactly the same way as they had milk in the beginning. Many of them develop skin hypersensitivity to that protein, which, in contrast to the milk protein, does not produce dermatitis.

These observations do not seem reasonable and are not easy to explain, but I have seen this sequence of events so many times that I believe they are probably correct.

Hypersensitivity to cow's milk is one of the common causes of atopic dermatitis in infants. It is, in contrast to the egg white sensitivity which is almost universally present in these infants, as a rule not of high degree. The infant is taking each day a large amount of the allergen to which he is sensitive; he is in reality undergoing immunization to milk protein and has dermatitis during the course of it. He has sometimes a positive scratch test to milk. If this is so, his dermatitis is almost certainly partly or entirely due to milk and will be almost certainly improved or cured by a milk-free diet. He is more likely, however, to have a negative scratch test and a positive intracutaneous test. If this is the case, his dermatitis may or may not be relieved by removal of milk. Some of the positive intracutaneous milk tests have no more significance than the positive soybean tests.

Clinical milk sensitivity in eczematous infants is, as a rule, but not always, a transitory phenomenon. After a few months of a milk-free diet, milk may be resumed usually without recurrence of dermatitis or other evidence of clinical sensitivity. The positive skin tests, however, are likely to persist for a long time, sometimes for years after the clinical sensitivity has been lost. The soybean reactions, likewise, are of long duration and are not analogous to the positive skin tests which Schloss found after the ingestion of a new food in normal young infants and which lasted only a very short time. One of our infants who developed soybean skin sensitivity still had a positive test three years after he had stopped eating soybean; another, ten months after; another who was still taking it, eighteen months after the first positive test; two others, five months afterward. The question arises whether those infants who have developed skin hypersensitivity to soybean in early life are likely later to have allergic symptoms from soybean, which

is now found in so many foods. I can say only that to date I have seen no evidence to affirm this and some to deny it. One infant was fed soybean for several weeks and developed a positive test. He returned about three months later, having had no soybean food in the interim. He was then put back on soybean, with considerable improvement in his skin, and developed no new allergic symptoms. Those eczematous infants who are deprived of milk or wheat for a considerable period never develop severe allergic symptoms when they resume the food. If it is removed too soon, there may be possibly a return of the dermatitis, but no more. The sensitivity of most of these infants is not of high degree—it can in no way be compared to that of the person who can take none of the food to which he is sensitized, such as those persons who are exquisitely sensitive to fish or nuts or to those infants who are sent into shock when they take for the first time a small amount of cow's milk.

Is there any essential difference immunologically between the soybean and milk reactions? I doubt it. The average size of the soybean reactions was possibly a little smaller than those of the milk reactions. I have seen no positive scratch tests to soybean. Some of the intracutaneous tests were, however, of good size, with wheals over 1 cm. in diameter, and small pseudopods. One boy is of particular interest. As an infant he gave a large intracutaneous milk test. He was put on soybean food, with prompt disappearance of an extensive dermatitis. He developed a soy bean reaction of equal size to the milk reaction but kept on eating soybean for over two years, with no dermatitis.

During this period, hyposensitization to milk by the oral method was attempted several times but had to be discontinued because dermatitis and urticaria developed, even with small amounts of milk. Finally, when he was 3 years old, hyposensitization to milk went along without any difficulty, and he is now, at the age of 5 years, taking a normal amount of milk, with no dermatitis. He still has large positive skin tests (of about equal size), to lactalbumin and soybean. He also has ragweed hay fever. Whether the "hyposensitization" really did him any good or whether with increasing age he stopped absorbing milk protein is a question.

Reagins were absent in the three soybean cases tested. In fifteen other cases with positive intracutaneous tests to milk, not included in the series under discussion, reagins were present in eight and absent in seven. I have had the impression that a positive skin test to milk in eczematous infants is more likely to be of clinical significance if accompanied by reagins. Chobot and Hurwitz[1] controlled observations have shown, however, that the presence or absence of reagins has nothing to do with the presence or absence of clinical sensitivity.

I have no satisfactory explanation for these soybean reactions. It would be explanatory to say that soybean protein is a poor antigen, but this is not so, for instances of exquisite sensitivity to soybean have been

reported. One possibly significant fact is that ingestion of the milk protein began in most cases when the infant was only a few days or a few weeks old. The soybean protein was first ingested, as a rule, between the fifth and eighth months. The digestive processes of infants during the first few weeks of life are not adequate to split large amounts of protein, and most infants with modern methods of feeding are fed large amounts from birth, thus suggesting the initial absorption in the milk cases of a large amount as a sensitizing dose. On the other hand, even at the age when the soybean protein was first ingested, it is certain that some of it was unsplit and absorbed, at any rate in the beginning, inasmuch as immunologic skin reactions developed. There are very great differences in the ease of absorption of different proteins. The most likely explanation of the lack of etiological significance of the soybean tests is that soybean protein may be considerably less easily absorbed than lactalbumin, that, while enough of it was absorbed to produce initial skin sensitization, not enough was absorbed thereafter to produce an eczematous reaction in the sensitized skin, and furthermore, that the degree of skin sensitization was not high enough to produce dermatitis unless a considerable amount was absorbed. The concentration of protein used for intracutaneous skin tests probably is often in great excess over that circulating in the blood stream after the ingestion of food which does not produce clinical symptoms.

Whatever the explanation may be, the genesis of entirely nonetiological skin sensitivity to foods in atopic persons is demonstrated. It seems likely that many of the positive skin tests to foods in atopic dermatitis, or indeed in any allergic condition, particularly if obtained by the intracutaneous method, are analogous to these soybean reactions and are of no more clinical significance than Colmes, Guild, and Rackemann's[2] positive grain reactions in normal bakers.

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CONTACT DERMATITIS FROM THE NARROW LEAF MARSH ELDER (IVA ANGUSTIFOLIA)

Observations on the Dermatitis-Producing Factor

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DERMATITIS of the contact type from at least one member of the genus Iva was mentioned by Huber and Harsh in 1931,[1] who reported two patients in whom dermatitis was caused by contact with burweed marsh elder *(Iva xanthifolia)*. It is the purpose of this paper to discuss the narrow leaf marsh elder *(Iva angustifolia)* as a common cause of contact dermatitis in Texas.

BOTANICAL

According to the classification of Rydberg,[2] the marsh elders occurring in North America are as follows:

Iva	*ciliata*	Willd.*
	caudata	Small
	microcephala	Nutt.
	angustifolia	Nutt.*
	asperifolia	Less.
	oraria	Bart.
	frutescens	L.*
	hayesiana	A. Gray
	cheiranthifolia	H. B. K.
	axillaris	Pursh*
	imbricata	Walt.
Cyclachaena	*xanthifolia*	(Nutt.) Fresn.*
	pedicellata	Rydberg*
	ambrosiaefolia	(A. Gray) B. & H.*
	Lobata	Rydberg

Most botanists include the last four in the genus Iva, but Rydberg maintains that they should constitute a separate genus. The morphology of the pollen grains and many other characters of the plant indicate the correctness of Rydberg's point of view. However, they are all commonly called marsh elder.[3]

The narrow leaf marsh elder *(Iva angustifolia)* (Fig. 1) is described by Parks and Cory[4] as growing in five of seven sections of Texas, leaving out only the mountainous region of west Texas and the Panhandle. Small[5] states that it grows in abundance in the river-bottom

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*Listed by Parks and Cory as occurring in Texas.

lands of Arkansas, Louisiana, and Texas. This author gives the following botanical description:

> Annual, strigose or hirsute-strigose. Stems erect, or ascending, 5 to 12 cm. tall, branching above, leaves various, blades linear or linear-lanceolate, 4 to 6 cm. long, or the upper 2 to 4 cm. long, narrowly linear or linear filiform, acute, entire or sparingly toothed, ciliate; heads numerous, often crowded brachts narrowly linear or linear-filiform; involucre turbinate, 3 cm. high bristly; bracts partially united into a cup, the free portion ciliate, fructiferous flowers solitary; corolla, 3 cm. long; lobe ovate, acutish, recurved, achenes cuneate-obovate, 3 cm. long.

Actually, *Iva angustifolia* is a very common weed in southeast Texas, particularly in the cut-over rice fields. It varies in size from 3 to 4 inches with one slender stalk to as high as 2 to 4 feet with a markedly branching stalk. The size of the weed seems to depend upon the soil and the thickness with which it grows. When the weeds are closely packed in marshy earth, they rarely grow higher than 8 to 12 inches, whereas in richer land where they are not so closely packed they attain much greater size. *Iva angustifolia* follows the usual course of the ragweed tribe in that it blooms in the fall and produces great quantities of pollen. This pollen is very light and has severe inhalant sensitizing characteristics, producing hay fever and asthma in susceptible individuals.

CLINICAL OBSERVATIONS

Dermatitis from *Iva angustifolia* assumes the definite clinical picture of weed dermatitis, the eruption first involving exposed areas such as the ankles, hands, neck, and face. It usually begins around the ankles and appears later on the hands, eyelids, and face, and often in the cubital and popliteal spaces. The condition may eventually become generalized and involve the complete skin surface, including the scalp. The mucous membranes of the lips and glans penis are occasionally involved. As a general rule this dermatitis begins in early spring and disappears with cold weather, but with each year the period of clearing in the winter becomes shorter until it assumes a perennial course.

The eruption itself presents an erythema with swelling and intense pruritus. Following massive exposure it may become truly vesicular with weeping and oozing. The condition is usually eczematoid in the chronic cases. Occasionally, we find a patchy dermatitis with apparently normal skin in between. We have one patient in whom the eruption appeared to be follicular in type; so much so, in fact, that when he was presented before the Texas Dermatological Society the idea was advanced that the condition might be due to the paraffin base in lubricants he used and with which he came in contact in the petroleum industry, or to a possible avitaminosis.

As was proved by Shelmire with poison ivy,[6] dermatitis due to *Iva angustifolia* is apparently caused by direct contact with the weed or

with some intermediate object, such as shoes, wagon wheels, cows' udders, etc. We do not believe that coming in close contact without actually getting some of the oleoresin on the skin will produce a dermatitis. To substantiate this opinion, we placed an open pan containing the fresh weeds in the bedroom of an individual sensitive by patch test to a dilution of 1:1,000,000 and he developed no dermatitis; dropping one small leaf on his abdomen while he slept and leaving it there only thirty minutes produced a severe dermatitis. We also burned *Iva angustifolia* and had this individual hold his arm in the smoke for a period of several minutes without producing a dermatitis. Furthermore, the oleoresin seems to be destroyed by actual burning, as we obtained a negative patch test from the ash. Steam from a boiling watery extract of *Iva angustifolia* likewise failed to produce a dermatitis on this man's arm; neither did we get a positive patch test with a distillate of any of the solutions.

Fig. 1.—*Iva angustifolia* plant of average size, before blooming.

We feel reasonably certain that the dermatitis-producing factor of this weed is distributed over the body by manual contact. One patient, tested many times with various concentrations, always developed a generalized dermatitis after each patch testing; but when patch tests were applied to unbroken skin and covered so that he could not get small amounts of the excitant beneath his fingernails and thus spread it to another part of his body he did not get a generalized dermatitis, although he did have a severe patch test reaction.

SPECIFICITY

The reaction from *Iva angustifolia* represents a true sensitization. Many plants, such as poison ivy, and *Euphorbia marginatum*,[7] are said to produce an irritative reaction in addition, but we have not found this to be true of *Iva angustifolia*.

Of approximately 100 patients with clinical histories of weed dermatitis and positive patch tests, twenty-four were found sensitive to *Iva angustifolia*.

Subclinical Sensitivity.—Of the twenty-four patients sensitive by patch tests to *Iva angustifolia*, we thought three had only subclinical sensitivity. One of these patients had a very definite history of recurrent attacks and a true clinical picture of poison ivy dermatitis. He worked with a seismograph crew where he frequently came in contact with poison ivy, and his attacks would last the usual two to three weeks. On routine patch testing for weeds, we found that he gave an erythematous reaction from *Iva angustifolia*, in addition to a positive test from poison ivy, but he had never developed a typical weed dermatitis as described. We think, however, that if in the future this individual comes in contact with weeds in this part of the country, he will eventually develop a clinical dermatitis due to *Iva angustifolia*.

Of the twenty-four patients, five were sensitive to *Iva angustifolia* alone. The other nineteen presented multiple sensitivity varying from two to fourteen weeds. The average age was 45 years, and the duration of the dermatitis varied from a few months to seventeen years.

We did not find a great deal of relationship between inhalant allergy and contact dermatitis due to *Iva angustifolia*. The number of patients with a history of asthma and hay fever was no greater than in the ordinary run of dermatologic cases.

METHOD OF EXTRACTION

The oleoresin was recovered from the dried plants by ether extraction at first according to the simple process of adding enough ether to the ground leaves and small stems to entirely cover them and allowing the extraction to proceed overnight in a closed wide-mouth fruit jar. Later an extraction apparatus was devised which seemed to give better yields and to afford a great economy of ether (Fig. 2). The ether extract was filtered through a good grade paper to remove coarse debris as well as a relatively large amount of finely divided particles which we took to be silica, the filtered ether extract being received into weighed Erlenmeyer flasks. After removal of the ether by distillation, the oleoresin was diluted to 1 per cent with acetone for routine patch testing according to the technique suggested by Shelmire.[6] It was found that all the ether-extractable fraction of *Iva angustifolia* was

highly soluble in acetone and a 10 per cent concentration was selected for storage of stock material.

For patch testing the 1 per cent acetone extract was applied to unbroken skin and the site left uncovered. All tests were read within forty-eight hours, but they were always watched from five to seven days, as occasionally a late reaction was seen. Positive tests remained from a few days to several weeks. As in patch tests with other substances, various degrees of reaction were encountered, ranging from erythema with mild thickening and eventual scaling limited to the area actually covered by the test substance to marked induration and spreading over several centimeters and even to vesiculation.

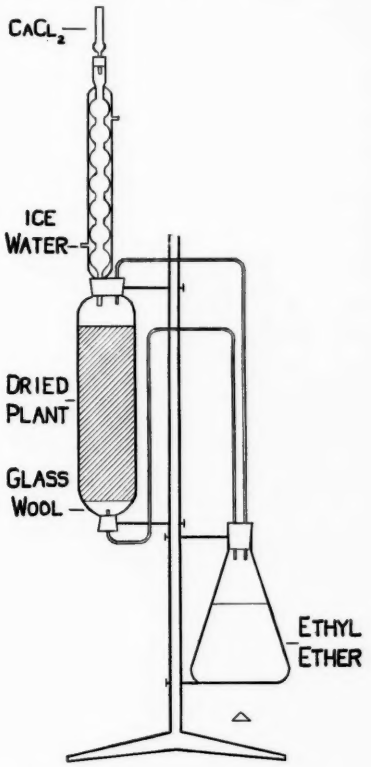

Fig. 2.—Extraction apparatus for recovery of ether-soluble oleoresins from dried plants.

The percentage of oleoresin in *Iva angustifolia* was found to vary somewhat according to the part of the plant from which it was extracted. Extraction with ether in the apparatus mentioned above of one specimen collected during the fall months revealed the following percentages:

From leaves and flowering heads	12.5% oleoresin
From leaves	5.8% oleoresin
From stems	1.2% oleoresin

The dermatitis-producing factor seems to occur in the heads, the leaves, the stalks, and the roots. We have routinely ground up the entire plants for extraction.

SENSITIZING FACTOR

To our surprise, we have found that the skin-sensitizing fraction of *Iva angustifolia* is soluble not only in ether, alcohol, and acetone, but also in hypertonic saline solution, glycerin, cold water, and boiling water. Patch tests done on sensitive individuals were positive with all of these extractions. A mixture of glycerin and hypertonic saline solution[9] seemed to extract more of the excitant than any other solvent and gave more pronounced reactions. Such an extract prepared in 1936 is still quite potent. Furthermore, a simple aqueous extract of the plant is still active after eighteen months. It appears, therefore, that aqueous extracts of *Iva angustifolia* do not become impotent after a few weeks as do similar extracts of many other plants.

A watery extract of *Iva angustifolia* was subjected to dialysis through a cellophane membrane, and it was found that the dialysate contained the dermatitis-producing factor. This would seem to indicate first that this factor is of relatively small molecular structure, and secondly that it may exist independently of the oleoresin. The aqueous extract was thermostabile, being unaffected by boiling.

A 10-Gm. portion of the oleoresin was added to 50 c.c. of 10 per cent sodium hydroxide, and the mixture was boiled several hours, the volume being kept constant by addition of small amounts of water from time to time. When the mixture was cool, it was thoroughly shaken with an equal amount of ethyl ether in a separatory funnel, and after several hours the ether and aqueous fractions were separated; similar washing with ether was repeated six times. All the ether portions were pooled and the ether distilled away, leaving a light amber-colored residue, presumably of unsaponifiable waxes, resins, or oils. The alkaline aqueous fraction was treated to saturation with sodium chloride, and the soap thus salted out was recovered on filter paper. To be sure all the soap was removed, the salt solution was further concentrated by boiling and again filtered after it was cool. The soap collected on filter paper was washed with saturated sodium chloride solution until the washings were colorless, in order to remove all the lye and coloring matter possible; the washings were added to the alkaline saturated salt solution. The soap was dissolved in distilled water and dialyzed against several changes of water until testing with silver nitrate solution showed all the salt to be removed. After evaporation to dryness, the soap was dissolved in water to make a 1 per cent solution for patch testing. The alkaline-saturated salt solution, containing now only the by-products of saponification without the unsaponifiable materials, was neutralized with hydrochloric acid, whereupon two precipitates were formed, one a fine white material, the other a black gummy substance.

Both precipitates were collected on the same paper and washed with several changes of saturated salt solution; then just enough water was added to dissolve the dark fraction so that it passed through the paper in solution. Addition of salt to the dissolved dark material caused reprecipitation; collection was accomplished by centrifugation. The white precipitate was washed with small quantities of cold water, then allowed to dry on the paper. We have not determined the nature of this precipitate; it was insoluble in alcohol, ether, and acetone, but was slightly soluble in warm water. The dark precipitate is likewise an unknown substance. The neutralized salt solution was not further treated.

Patch testing performed with all the products of the saponification experiment were negative, except with the neutralized salt solution which gave strongly positive tests. Hence, we concluded that the excitant is not affected by alkalies, and that it is not contained in the saponifiable or unsaponifiable oils, waxes, or resins.

DISCUSSION

The skin-sensitizing factor of *Iva angustifolia* is apparently not an oleoresinous material, although it is extractable from the leaves, stems, and roots of the plant along with the ether-extractable oleoresins and waxes. The same or a similar factor is also water soluble and quite stabile in aqueous solution, although hypertonic-glycerin solutions in our experience afford stronger activity and greater permanency than plain aqueous solutions. We have wondered whether we were dealing with a conjugated substance composed possibly of a small protein molecule loosely joined to a lipid. If this is true, only the small molecule is soluble in water, in which solution it is readily dialyzable, whereas the entire conjugated product may be soluble in such solvents as ether and acetone. The possibility remains that further work may identify this substance in its pure form.

TREATMENT

Treatment consists primarily in avoidance of the plant. Patients must become weed conscious and must be shown the weeds to which they are sensitive. There are some individuals whose environments and occupations are such that they cannot help but come in contact with weeds, while others can remain free from symptoms by avoiding only heavy exposure. One patient, a carpenter, came in with severe dermatitis in September, 1939. His trouble had begun four months previously; he was sensitive on patch testing to *Iva angustifolia, Parthenium hysterophorus,* ragweed, and cocklebur. The eruption lasted until the weeds disappeared in the winter. During the summer of 1940 this man, although still working, was able to stay well because he took particular care not to contact weeds or to handle his shoes or clothing which

might have come in contact with weeds. He came in at our request in April, 1941; he still gave a positive patch test to *Iva angustifolia*. We do not consider him as having only subclinical sensitivity but as having successfully avoided weed contact. We have other patients who were relieved by the elimination of weeds from their environment.

Several years ago we took up the matter of desensitization with injections of the oleoresin in alcoholic solution. Following the method of Spain in desensitizing for poison ivy, we started with 0.10 c.c. of 1:10,000 dilution, then gave 0.10 c.c. of 1:1,000, and so on to 0.10 c.c. of 1:10, at appropriate intervals. We carried one patient through the winter with treatment along these lines, but at the beginning of spring he immediately broke out and his patch tests were just as markedly positive as they were at the beginning of treatment. From our experience with this and other cases, we do not believe it is possible to get sufficient protection with this method. Furthermore, we find the injections of little value when given during the eruption.

Following a personal communication with Shelmire in 1939, we began giving our patients the oleoresin by mouth. We gave them a 10 per cent solution of *Iva angustifolia* oleoresin in oil, using capsules for administration, beginning with 1 drop and increasing to as much as 20 drops per day. We feel that we have helped a considerable number of these people, although their positive patch tests have been altered very little by the treatment. Some few individuals do not seem able to tolerate the oleoresin by mouth in amounts sufficient to desensitize them. Others can take from 15 to 20 drops with ease; we think we might expect to get some desensitization eventually in these individuals, particularly since the publication of Shelmire's work on desensitization with poison ivy.[8] Frankly, however, we do not feel at this time that we accomplished a great deal in actually desensitizing these persons, but we feel that our efforts are in the right direction and that we should be able to offer them more relief by use of the excitant by mouth when dosage is definitely standardized.

SUMMARY

1. *Iva angustifolia* is one of our major skin sensitizing weeds, and it produces severe dermatitis in sensitive individuals.

2. The dermatitis-producing factor or chemical excitant present in *Iva angustifolia* is not an oleoresin, although it may be extracted along with the oleoresin.

3. Treatment consists of avoiding the weed and of giving the excitant in the form of ether-extractable oleoresins by mouth and of indicated local dermatologic therapy.

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CONTAMINATION OF ANTIGENS WITH TRACES OF OTHER ANTIGENS AS A CAUSE OF FALSE POSITIVE REACTIONS IN INTRADERMAL TESTING

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THE reliability of the intradermal method of skin testing in allergy has been much criticized because of the large number of "false positive" reactions obtained with its use. A known factor in producing such false reactions is the contamination of test antigens. This report describes experiments showing the urgent importance of attention to every possible source of contamination and practical techniques for avoiding some of them.

The reason contamination is important is that some skins are extremely sensitive. We have found that patients who react by intradermal test to 1:1,000,000 extracts are fairly common, and we have one patient who gives a specific, reproducible reaction to a 1:1,000,000,000 extract of a Brazil nut concentrate containing about 80 per cent of extractable protein (tungstic acid precipitation). Since only about 0.01 ml. of this dilution was injected, her skin will easily detect 10^{-11} Gm. of protein.

It is evident that any failure to clean equipment thoroughly between one solution and the next will result in confusing and erroneous results. We have studied the influence of several potential sources of contamination and have attempted to determine the degree of contamination which may be introduced by usual procedures.

CLEANING METHODS

All equipment not otherwise described below was prepared by the following methods:

Syringes.—Let stand overnight, with plunger and barrel separated, completely immersed in bichromate-sulfuric acid cleaning solution (25 Gm. of sodium bichromate dissolved in 1 liter of commercial sulfuric acid); rinsed thoroughly in running tap water, then in distilled water.

Needles.—Boiled in 1 per cent trisodium phosphate solution ten minutes, held for thirty minutes to permit the hot solution to penetrate the lumens of the needles, which may be filled with steam during the

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boiling, again brought to a boil, rinsed thoroughly in tap water, brought to a boil in dilute (approximately 0.001 molal) pH 6.0 phosphate buffer and held overnight in this solution, rinsed in distilled water, wrapped in clean towels, and steam sterilized.*

Bottles.—Boiled ten minutes while completely immersed in 1 per cent trisodium phosphate solution, allowed to cool for one hour to permit the bottles to fill with solution, again brought to a boil, then rinsed once in dilute (N/10) hydrochloric acid, four times in hot tap water, and finally in distilled water, allowed to drain thoroughly, then sterilized by dry heat at 160° C. for two hours.

Solutions.—Prepared with chemically pure reagents and distilled water in flasks and bottles cleaned by scrubbing with soap and water and rinsing in distilled water. Sterilized by filtration through Seitz filters, the metal and rubber parts of which were cleaned by boiling in 1 per cent trisodium phosphate solution and rinsing in distilled water.

TEST RESULTS

First Experiment.—Four clean syringes were deliberately contaminated by being filled with 1:1,000 egg white allergen solution and held for an hour. The solution was squirted out and the syringes rinsed twice by drawing up distilled water and squirting it out. They were then boiled in clean tap water in a large sterilizer and allowed to cool between sterile towels. Pure sterile "control" solution (0.8 per cent sodium chloride, buffered at pH 7.4 with 0.0075 molal potassium phosphate, containing 2.5 per cent glycerine, and 1:50,000 phenylmercuric acetate preservative) was filled into these and into six clean steam-sterilized syringes fifteen minutes before the start of testing.

Forty-five allergic children were tested, each with six sites from clean and four sites from the "contaminated" syringes. With the contaminated syringes, out of 180 sites, forty-five positive reactions (25 per cent) occurred, several of which were large and all of which were on children who were shown by repeated testing to be skin-sensitive to egg white. With the clean syringes, out of 270 sites, five reactions (1.9 per cent) occurred, three of which were on one child and all of which were borderline.

Second Experiment.—This experiment had for its object the determination of the relative contribution of some of the factors involved toward the production of false reactions. Five children were selected for their high degree of sensitivity to certain materials as indicated by marked scratch reactions with 1:50 extracts. Their degree of skin sensitivity by

*We now have improved the method of cleaning needles so that it is much less work and also less prone to dull the points. After use they are inserted in two rows down the sides of a short piece of large diameter gum rubber tubing closed at one end by a short piece of glass rod. The other end is attached by glass and rubber tubing to a water aspirator filter pump. The alkaline cleansing solution, tap water, and distilled water are drawn in turn through the needles, draining and drawing air through after each immersion. Any needles which may be plugged are removed and set aside for individual attention and the tube with needles still attached is wrapped in paper for sterilization. To avoid plugging the needles, the solutions must be clear and protected from dust.

intradermal test was roughly measured by a titration with serial tenfold dilutions of these allergen solutions, using clean equipment and technique throughout. Dilutions were made by transferring 0.5 ml. of solution into 4.5 ml. of saline, using a fresh syringe for every second transfer and rinsing the syringe thoroughly with the middle dilution but not at all with the first and last. The results of these tests are given in the upper section of Table I.

Parts of the equipment necessary to the intradermal test were then contaminated in various ways, as indicated below. Each individual item was contaminated with but one allergen and was subsequently used to inject "control" solution which would otherwise have been free of intentional contamination. The results are shown in the lower section of Table I.

Preparation of Equipment.—

For sites 1 and 2: *Clean equipment* and pure "control" solution.

For sites 3 and 4: *Needle contamination.* Needles were attached to syringes which were filled with 1:1,000 extract (e.g., two with cat hair for LM, two with mustard and two with peanut for LT, etc.), then rinsed with water. They were transferred to clean syringes, and after sterilizing by boiling in clean tap water for five minutes, they were filled with clean "control" solution fifteen minutes before use.

For sites 5 and 6: *Needle contamination.* Same as for sites 3 and 4 except that the water rinse was omitted.

For sites 7 and 8: *Syringe contamination.* Clean syringes were filled with the appropriate 1:1,000 extracts, rinsed in a stream of warm tap water with the plunger withdrawn for about five seconds, then again in distilled water by drawing it up and ejecting it. Clean needles were attached and the whole sterilized by boiling in clean water for five minutes.

For sites 9 and 10: *Bottle contamination.* Antigen bottles in which 1:1,000 extracts of the appropriate allergens had been stored, in some cases for many months, were emptied, rinsed in tap water three times, in distilled water once, then drained and sterilized dry at 160° C. for two hours. After cooling they were filled with clean sterile control solution, stoppered with new rubber caps, and held several hours at room temperature before filling clean syringes for the injections.

For sites 11 and 12: *Bottle contamination control:* Other such bottles were cleaned as described under "cleaning methods," sterilized along with those for sites 9 and 10, and subsequently handled in the same way.

By comparing the two sections of Table I it is seen that in three instances the contaminated syringes were carrying antigen sufficient to produce reactions equal to or stronger than those obtained in the same patients with 1:100,000 (10^{-5}) dilutions, while the needles and bottles produced reactions equal to or larger than those obtained with a tenth

of this strength. Comparison of tracings of the reactions, made on cellophane, gave the same results, eliminating the possibility that estimates of reaction degree might have varied between the tests.

TABLE I

EVALUATION OF CONTAMINATION FROM VARIOUS SOURCES BY COMPARISON WITH KNOWN DILUTIONS

PATIENT	ALLERGEN	TEST DILUTION					
		10^{-4}	10^{-5}	10^{-6}	10^{-7}	10^{-8}	CONTROL
L. M.	Cat hair	–	4	2	0	–	0
L. T.	Mustard	–	4	3	2	–	0
	Peanut	–	3	2	0	–	0
W. L.	Cod	–	4	3	3	0	0
A. V.	Egg white	4	3	2	2	0	0

		EQUIPMENT CONTAMINATED											
		CONTROL		NEEDLES		NEEDLES (RINSED)		SYRINGES		BOTTLES		CLEANED BOTTLES	
	SITE:	1	2	3	4	5	6	7	8	9	10	11	12
L. M.	Cat hair	0	0	4	4	3	3	4	4	2	2	0	0
L. T.	Mustard	0	0	3	3	3	3	4	4	3	3	0	0
	Peanut	0	0	3	3	3	3	4	4	3	2	0	0
W. L.	Cod	0	0	0	0	2	2	4	4	3	3	0	0
A. V.	Egg white	0	0	0	2	3	0	0	0	0	0	0	0

Reaction Scale: 2, Definite positive, with wheal and flare; 3, large, but lacking well-defined pseudopods; 4, large, with well-defined pseudopods; –, not tested.

DISCUSSION

The concept that stable adsorbed films of antigen may cause erroneous results in skin tests is by no means new. In 1926 Smith[1] stated, "Tuberculin is not thermolabile and resists boiling indefinitely, therefore syringes and needles should not be used for Schick or other tests after being used for tuberculin." These observations were confirmed and extended by Nelson, Seibert, and Long.[2] In 1935 Rackemann and Simon[3] demonstrated that glass syringes were capable of adsorbing sufficient ragweed pollen extract to give false positive reactions on highly sensitive individuals. Simon[4] later re-emphasized the necessity for chemical cleanliness but suggested that dilutions of 1:100,000 or 1:1,000,000 are "probably beyond the range of apparent activity in skin testing," an assertion which is contradicted by our findings.

A sufficient number of allergenic substances have now been tested that it seems safe to say that it is the rule rather than the exception for such substances to form films on glass or metal apparatus which resist rinsing with water and survive sterilization by boiling or dry heat to a degree capable of causing reactions in many sensitive persons.

It is obvious that clinical intradermal testing done in neglect of this factor will result in numerous "false positive" reactions; that is, reactions to extracts of substances to which the patient is not at all sensitive, especially if he is strongly sensitive to some other substance on the testing list. To avoid errors and confusion, it is suggested that "control" solutions composed and treated exactly like the regular test

solutions, except for the omission of the allergen, be injected with all clinical tests and that reactions to these be read and recorded with the usual care and objectivity. Then if tabulation shows that definite reactions are occurring at more than 5 per cent of such control sites, search should be started at once to find the source of the trouble.

It is also probable that many of the contradictory results in the literature may be explained by lack of satisfactory control of contamination. This is especially true when experimental reactions are taken at their face value, without comparison with suitable controls, as is done for instance in some reports on new allergenic substances. In order to receive serious consideration, descriptions of work in which the intradermal test is used or studied should mention evidence of satisfactory control of contamination errors.

SUMMARY

1. Intradermal skin reactions in sensitive persons to control solution handled in syringes, needles, or bottles which had been deliberately contaminated with selected allergens and then rinsed and sterilized were compared with reactions to dilutions of the same allergens to give a roughly quantitative measure of each as a source of contamination. In most cases reactions as large or larger than those with 1:1,000,000 solutions were obtained.

2. Allergic persons capable of reacting to 1:1,000,000 extracts by intradermal test are not rare, and an occasional patient will react to one-thousandth of this strength.

3. Many allergens form stable films on glass or metal equipment which are not removed by rinsing or destroyed by sterilization.

4. Cleansing methods should be proved to be adequate by skin tests on sensitive persons. Adequate, practical methods are described.

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THE EFFECT OF ZINC ON THE STABILITY OF POLLEN TANNATE

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IN A previous report[1] on the treatment of hay fever with the precipitate obtained by adding tannic acid to pollen extract, it was stated that some of the precipitated pollen tannate apparently redissolved or dissociated when resuspended in buffered saline (Coca solution). This was indicated by the ability of sulfosalicylic acid to produce a precipitate when added to the clear supernatant fluid of such a suspension and by the positive skin reactions of the supernatant in sensitive patients. It was suggested that dissociation was decreased when zinc chloride was added to the pollen extract before tannic acid. The purpose of this communication is to confirm this and to report observations regarding the preparation of pollen tannate suspensions which prevent dissociation and change in color.

METHODS AND RESULTS

Ragweed pollen was defatted with ether or petroleum ether and then extracted in physiologic saline solution to make a 1:20 extract. After Seitz filtration, to each 100 c.c. of extract was addel 1 c.c. of a sterile 10 per cent zinc chloride solution in distilled water, followed by 5 c.c. of a sterile 10 per cent tannic acid solution in distilled water. After standing overnight, preferably in the cold, the supernatant was poured or siphoned off, the remainder centrifuged, and an equal volume (estimated) of sterile glycerin was added to the precipitate. Such preparations contained about 2 mg. of nitrogen per cubic centimeter, as determined by the micro-Kjeldahl method. They were gray or brown in color. Such preparations were called stock suspensions.

When stock suspensions were added to Coca solution to make a nitrogen concentration of 0.2 mg. per cubic centimeter, a white suspension appeared, which would settle on standing, leaving a clear colorless supernatant. After a few days, however, discoloration began and progressed to a deep yellow or brown. Stock suspensions diluted with saline alone showed no discoloration after months of use. It seems likely that the buffering phosphates in Coca solution caused a precipitation of insoluble zinc phosphate, removing the protective effect of the zinc in the protein combination.

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Suspensions in saline, containing 0.2 mg. of nitrogen per cubic centimeter, when tested by the scratch method showed reactions which appeared in the usual time, and were equal to, or slightly larger than, those produced by the regular 1:50 pollen extract in the same patients. To determine if any of the precipitated extract had gone back into solution, the precipitate was removed by Seitz filtration. The clear filtrate was treated with 5 per cent sulfosalicylic acid, and no precipitate appeared. The clear filtrate was then tested for activity in highly ragweed-sensitive patients, first by scratch test and then by intradermal injection. The scratch tests were negative. The intradermal tests showed negative or doubtful reactions in two patients who had large reactions to a 1:25,000 dilution of pollen extract. Evidently, no significant amount of the active principle was dissolved in the supernatant fluid.

The stabilizing effects of zinc on protamine insulin precipitate and on pollen tannate precipitate may be examples of a phenomenon applicable to other protein combinations. This warrants further investigation with zinc and other metals.

SUMMARY

1. Zinc chloride to a concentration of 0.1 per cent added to pollen extract before tannic acid prevents dissociation and discoloration of the precipitated pollen tannate.

2. In the preparation of zinc pollen tannate, the extracting and diluting fluids should contain only electrolytes, such as sodium chloride, which do not form insoluble zinc salts.

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ODORS (OSMYLS) AS ALLERGENIC AGENTS

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THE term "osmyl" has been coined by the science of osmics to denote any kind of odor, pleasant or unpleasant. Clinical and experimental evidence will be presented below to prove that osmyls can act as allergens in certain cases. Among these are the scents of flowers, fruits, resins, and the odors of foods of animal and plant origin as well as those of the animals themselves.

The French scientist Devaux[1] devised a method to prove that material particles emanate from odoriferous substances (Fig. 1). From these experiments he concluded that we smell a flower because minute particles originating from the petals strike the sensitive membranes of the nose.

SCENTS OF PLANT ORIGIN

Pollens undoubtedly head the list of allergens responsible for most hay fever cases. However, there are patients whose nasal symptoms or asthma appears in the vicinity of roses, locust trees, linden trees, mock-oranges, carnations, privet, lilies, common elders, lilacs, lilies of the valley, and violets.

Sticker[2] quoted several medieval physicians to whom it was well known that roses and their fragrance can cause sneezing and rhinorrhea in many people. Sticker as well as Mackenzie[3] observed cases where nothing but the odor of these flowers could have been the etiological agent. Of all the literature about the so-called "rose-cold" and "lilac-cold," only Sticker,[2] Feinberg,[4] Biederman,[5] Goodale,[6] and Urbach[7] have offered experimental evidence to show that volatile agents rather than pollen can be the cause of allergic symptoms.

The pollen etiology of a rhinorrhea can be excluded in the following instances: (1) if the blossoms in question have no stamens, and thus no pollen, since the stamens are transformed into petals (this is true of many grafted garden roses and lilacs); (2) if, as in Robinia, the peculiar position of the stamens surrounded by a carina makes it impossible for the pollen to be carried off by the wind; (3) if insufflation of the particular pollen into the nostril of the patient elicits no symptoms.

Several clinical methods for demonstrating that odors and not pollens are operative have been devised.

1. Exposure to Fresh Blossoms.—If the history indicates that a given blossom, e.g., jasmine, may be the cause but nasal and cutaneous tests

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with the pollen are negative, the following test is of value. During the patient's absence a bunch of jasmine covered with several layers of very fine organdy is taken into his room at a time when he is free of symptoms. He is not permitted to enter until one-half hour has passed so that any pollen that might have been disseminated can settle down. If any symptoms can thus be elicited, it is proved that they were caused by the odor only; that is, by the ethereal oil of the flowers in question.

Fig. 1.—Photograph of the effect produced by the odor of a rose petal suspended over mercury dusted with talc, according to the technique of Devaux-Breitenbach. The dark area is due to displacement of the talc by minute particles originating from the petal, while the central outline represents the position of the petal. (From European Picture Service.)

2. Exposure to Extracts of Blossoms.—Outside the season, when no fresh material is available, it is rather difficult to perform direct odor tests. However, dried flowers, such as linden or pseudoacacia, can be extracted in a well-closed container so that the volatile ethereal oil cannot evaporate. The test is performed by having the patient smell this extract. A variation of this method is the employment of commercial

extracts or appropriately scented soaps. For example, one of my patients whose asthmatic attacks were traced to the odor of a pine forest developed the same symptoms when she was instructed to use pine needle extract in her bath or to wash with pine soap.

Besides hypersensitiveness to odoriferous buds and flowers, bushes, and trees, there also seems to be a hypersensitiveness to the essential oils of conifers as well as the resins of other trees. Thus, rhinopathies and asthma may be caused by coniferous trees in carpenters and woodworkers and by turpentine in housepainters. We mention also hypersensitiveness to the strongly odoriferous orris root oil (in scented soaps, toilet water, smelling salts, hair tonic), to essential oils of eucalyptus and camomile, both of which are used for inhalation, to aloe, valerian, parsley, hop, and dill, as well as to camphor, peppermint, and incense. Allergy to linseed oil, as described by Sticker, is less frequent.

It should be stated here that patients who are hypersensitive to the smell of blossoms but not to their pollen frequently show a hypersensitiveness to other pollen; for instance, those of grasses.

Finally, allergy to the smell of vegetable foods has to be kept in mind. The hypersensitiveness may be elicited by the odor of the raw foodstuffs, such as garlic and onion, as observed by me. Henson[8] described garlic inhalation as the cause of asthma in a patient who worked in a sausage factory where powdered garlic was used. Sticker[2] reported the case of the Polish king Jagello in whom the smell of apples produced attacks of asthma. In other patients only the odor of foods during the process of cooking is operative. Thus Feinberg and Aries[4] reported instances of asthma due to volatile substances given off by peas, beans, and lentils during the process of cooking. To demonstrate the volatile nature of the reactive substance, Feinberg exposed shallow dishes of Coca's solution at distances of 30 inches and 5 feet, respectively, from a pot in which dried peas were being cooked. Skin testing with the first solution gave a definite reaction of the same degree as that of an extract of pea in a dilution of 1:10,000,000, while the second elicited only a faint reaction.

EXPERIMENTAL OBSERVATIONS

As mentioned above, I have observed cases of hay fever which were proved by the methods described above to be due to volatile oils. However, it has not been possible to determine which ingredients of the ethereal oils of the blossoms cause hay fever. Chemists are not yet able to fractionate the ethereal oils of roses, lilac, jasmine, etc., into *stable* constituents.* However, one might keep in mind the hypothesis that the

*Synthetic oils which imitate the odor of the plants in question cannot be used in these investigations as they are chemically entirely different from the natural ethereal oils.

unstable proteins which are present in the ethereal oils could be responsible for the allergenic effect.

It was decided, therefore, to study the problem on patients who were sensitive to other ethereal oils which were capable of chemical fractionation. We[7] had the opportunity of doing this on two patients with a strictly monovalent hypersensitiveness to sage tea.

The dried leaves of *Salvia officinalis* are used for gargles on account of their tannin content; besides tannin, sage tea contains sage oil, the known components of which are *d*- and *l*-camphor, α-thujone, sesquiterpene, zineol, and *l*-borneol; others are amaroids, resins, gumlike substances and inorganic compounds. The first patient exhibited swelling and inflammation of the oral mucosa when gargling with sage tea for the relief of toothache. She was asked to smell freshly brewed sage tea in a narrow-necked flask for two hours, at the end of which time objective and subjective signs of swelling in the nose appeared. Patch tests with 2 per cent aqueous, alcoholic, and etheric extracts of sage, as well as with the dried drug, caused local inflammation of the skin and the mucosa of the lips in the patient but not in control subjects. The introduction of a tampon saturated with a 2 per cent aqueous extract of sage into the nostrils caused nasal discharge and vivid reddening of the septal mucosa after approximately two hours. Thus it was proved that the allergenic principle was water soluble as well as ether soluble.

However, if the aqueous extract is boiled until the odor has completely disappeared, its capacity of eliciting reactions of the skin and mucosa is entirely lost. Sage oil by itself called forth no response, nor did the oil when extracted by steam distillation; this in spite of the fact that the patient invariably reacted to the aqueous extract of the drug. Even the application of sage oil on the nasal mucosa caused no reaction. We achieved the same negative result on application of the individual constituents of sage oil, such as α-thujone, *l*-borneol, zineol, 10 per cent chemically pure turpentine to represent the terpenes, diluted oil of camphor, and a 2 per cent tannin solution.

The results of these experiments eliminated sage oil itself as the allergen. Therefore, the following two possibilities were left:

1. The patient might be hypersensitive to a volatile substance contained in sage in spite of the fact that she failed to react to sage oil. It is known that if ethereal oils are distilled, substances are frequently obtained which differ markedly in odor from the original material. Furthermore, vapor of higher temperatures frequently destroys various labile substances.

2. The other possibility is that the patient might react to certain residual substances which remain after extraction but not react to

volatile components such as odors. However, here again we would have to be dealing with an unstable component which is destroyed by boiling, for no reaction could be observed upon application of the aqueous extract which had been subjected to boiling to a point where the odor of sage was lost.

To clarify this problem, the experiments described above were carried out. Smelling either a freshly brewed sage tea or the dried plant caused nasal reactions. Thus it must be concluded that odors contained in the sage plant represent the allergen.

To examine the question as to whether residual substances remaining after the extraction with petroleum ether could be the allergen, an aqueous extract of sage was prepared by a cold method and extracted with petroleum ether for eight days. At the conclusion of this process an aqueous (1) and a petroleum ether (2) component remained (Table I). The latter was redistilled and the resulting residuum (3) and distillate (4) were dissolved in 70 per cent alcohol for cutaneous testing, with the results shown in Table I.

TABLE I

PETROLEUM ETHER EXTRACTION OF A 2 PER CENT SAGE TEA PREPARED AT ROOM TEMPERATURE

Aqueous component (1) showed no reactions in the patients	Petroleum ether component (2) showed reactions in patients but not in controls	
	Residuum (3) showed no reaction in patients	Distillate (4) elicited very strong response in patients, so that applications had to be removed in three hours; some controls showed no reaction, some a slight one after an application for twenty-four hours

In a second experiment the petroleum ether solution was separated into volatile and nonvolatile components, using steam distillation for this purpose. Both of these were applied epidermally on patients and controls, using equal concentrations (2 per cent) in petroleum ether. The volatile fraction caused a very marked reaction in the patients while only occasional and very weak effects were seen in the controls. But even the almost odorless nonvolatile fraction caused a considerable skin reaction in the woman hypersensitive to sage, but not in controls.

Thus the experiment demonstrates that the allergen in question is soluble in petroleum ether and volatile on steam distillation.

The results of the smelling tests and the cutaneous tests, with fractions of petroleum ether extract of the drug, as well as with the individual components of sage oil, constitute the evidence that we are dealing with a specific and as yet unknown component of the essential

sage oil. It seems likely that the odoriferous substances contained therein represent the allergen in question.

A similar condition was found in a woman, aged 27 years, who developed a severe stomatitis with edema of the uvula and the soft palate on gargling with sage tea. A detailed description of her history seems superfluous, as her cutaneous and nasal reactions corresponded with those of the above case.

Another observation was made on a woman who was subject to severe sneezing attacks and rhinorrhea when peeling lemons. Upon introduction of a piece of lemon peel into her nose, she experienced instantaneous itching and rhinorrhea, although controls did not show any reactions. The application of lemon peel to the skin in aqueous, alcoholic, and etheric extracts was negative. Positive results were also encountered upon introduction of orange and tangerine peels into the nose, but no skin reactions could be produced. Thus we are dealing with a purely nasal hypersensitiveness to the essential oil of the group aurantiae (lemons, tangerines, and oranges).

I also treated a woman who developed severe rhinopathy and asthma a few weeks after accepting a position in a coffee store. Twenty-four hours after hospitalization her attacks disappeared although no treatment had been instituted. Smelling a small bag of coffee for only three minutes caused severe nasal and bronchial attacks after a very short time.

SCENT OF ANIMAL ORIGIN

It has been proved by a great number of observations that some patients develop allergic symptoms from the mere odor of certain animals without coming into actual contact with them. The animals involved in these observations include horses, cattle, dogs, cats, monkeys, sheep, mountain goats, hares, rabbits, guinea pigs, rats, mice, hens, and even bees, toads, and eels. For some persons allergic to the smell of dogs, the proximity of an individual owning a dog is sufficient stimulus to provoke an attack. De Besche[9] has studied this question experimentally. He extracted the characteristic odorous substance from horse urine and placed an open bottle of it in a room of horse asthmatics. Most of them promptly developed their asthma.

A patient treated by me illustrates the degree which such a hypersensitiveness can reach. It concerns a woman, aged 30 years, who regularly developed extensive angioneurotic edemas which usually were followed by severe anaphylactic collapse when she passed a street in which a fish market was located. A similar instance is that of a farmer who regularly suffered an attack of asthma when a west wind set in and carried the smell of horses from a stable which was located a few hundred feet to the west of the farmer's house.

In general, persons hypersensitive to the odor of animals are also susceptible to direct contact with them. However, there are certain exceptions. For instance, it is reported that patients allergic to horses may not be hypersensitive to horse dander and hair. This suggests that the allergen is the volatile substances produced by the sweat and apocrine glands of the skin. Despite the absence of the proper chemical experiments, I am of the opinion that these emanations contain, among other substances, some highly specific proteins which are the carriers of the hypersensitiveness.

Finally, this group also includes patients who are so hypersensitive to animal protein that even the smell of the particular food elicits symptoms identical with those appearing after its actual ingestion. In this connection, Sutton[10] and Decker[11] have described patients with hypersensitiveness to egg albumen who developed anaphylaxis when merely present in a room where an egg was being opened. Kämmerer[12] reports the appearance of swelling of the eyelids and conjunctivitis from the mere smell of fish; Lewis and Grant[13] even observed edema over the entire body in such a case. Boss[14] and I saw typical asthmatic attacks and urticaria in similar instances. Feinberg and Aries[4] reported a case of asthma due to the odor of cooking shrimps. As an enlightening example of what I would like to term "materialization of scents," we may mention Vaughan's[15] observation. A man hypersensitive to salmon was eating a salmon croquette to which he promptly reacted with an attack of asthma. The cook took the remaining croquettes to the refrigerator where he stored them near a package of butter, so that on the next day the butter tasted of salmon; on eating some of this butter, the patient had another attack.

SCENT OF OTHER ORIGIN

We have but little knowledge of allergic phenomena caused by scents other than of plant and animal origin. The third group includes inorganic and organic chemical compounds with the exception of essential oils of plants and proteins in animal emanations which are discussed above. Among the inorganic compounds are found certain synthetic perfumes which are frequently employed in cosmetics and soaps and which occasionally are responsible for asthma. As another example, a specific hypersensitiveness to sulfuric emanation in a sulfur spa was observed by me.

Somewhat more thoroughly studied is the hypersensitiveness to organic compounds. Thus Rappaport and Hoffman[16] reported a case of urticaria due to inhalation of aliphatic, nonconjugated aldehydes, such as acrolein, resulting from the oxidation of fats (glycerol in cigarettes, oxidation of the fatty oils in the frying of foods), and of formaldehyde with which the patient was in occupational contact.

To this group belong also cases of specific hypersensitiveness to burning wood, charcoal, and kerosene and to tobacco smoke. Duke[17] reports the case of a woman who was sensitized by the smell of a pile of charcoal burning below her window. Since then she has been hypersensitive to open charcoal stoves. A case of respiratory allergy to the smoke of brown coal and another to kerosene have been observed by me when the patients have been sensitized after protracted inhalation. Duke,[17] Rappaport and Hecht[18] have described asthma in firemen produced by hypersensitiveness to the smoke of wood.

Obviously in each individual case it is difficult to prove whether an asthmatic patient is irritated by the smoke in a specific or unspecific manner, or, even when his hypersensitiveness is definitely specific, whether he is sensitive to the odoriferous substances (osmyls) or to other chemical agents.

EXPERIMENTS ON ORAL DESENSITIZATION

The therapeutic results achieved support the evidence that at least in allergies to the smell of flowers the allergen is represented by odoriferous substances or volatile oils. Desensitization of the patient by the oral administration of minute doses of these oils has been successfully performed.

The essential oils of locust, jasmine, linden, etc. cannot be recovered from the blossoms by the usual chemical methods. I have therefore, made use of enfleurage, which is almost exclusively employed in the extraction of natural perfumes. Wooden boards are covered thickly with lard and the blossoms, for example, of the locust, are placed between them and are left for seventy-two hours. The blossoms are replaced from time to time. The lard takes on the smell and taste of the locust. The material processed in this way was used for oral administration in a patient who was specifically hypersensitive to locust and who suffered from severe attacks of "hay fever" during their blossoming time. The dosage employed was 2 Gm., four times daily, for two weeks. Thereafter, the patient, although living in a locust grove, became absolutely free from symptoms. She was also free from symptoms during the ensuing year after again taking her "locust butter" for four weeks prior to the season.

The objection could be raised that, during the manipulation required for the process for enfleurage, pollen could come into contact with the fat and so be responsible for the therapeutic success. However, the patient showed a negative reaction when tested nasally with locust pollen. A small amount of the fat containing the essential oil of locust was introduced into the patient's nose by means of an applicator, as was also pure lard. While the latter was completely ineffective, the former promptly elicited the symptoms of hay fever, but only in the

patient and not in the control subjects. Thus it was demonstrated that in this particular case the essential oil of the blossom and not the pollen was the responsible allergen.

In cases of hypersensitiveness to a volatile oil, as, for instance, turpentine, the specific oil can be administered directly in minute oral doses, as done by Perutz.[19] This is the same principle which is now so successfully employed in the desensitization of patients to poison ivy by the use of specific oleoresin (Shelmire[20]) and of contact dermatitis due to ragweed by ragweed oil (Sheldon and Blumenthal[21]).

SUMMARY

1. On the basis of chemical, physical, and physiologic observations, it appears that scent, whether organic or inorganic in origin, has a physicochemical basis and is propagated by minute particles. Accordingly, osmyls, as these odoriferous particles are termed, can act as allergens on inhalation in certain cases.

2. Hypersensitiveness to the scent of some trees and plants without associated hypersensitiveness to their pollen may explain the failure of pollen extract therapy in such cases.

3. A method of oral administration of substances prepared by the process of enfleurage is described for the treatment of scent allergies.

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TREATMENT OF ASTHMATIC PAROXYSM WITH NICOTINIC ACID

Preliminary Report

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VASODILATOR drugs, such as aminophyllin and strontium bromide, are being used intravenously for the relief of the asthmatic paroxysm. The marked vasodilator properties of nicotinic acid suggested its use in the treatment of asthma.

Since June, 1941, a group of thirty severe ambulatory patients attending the adult allergy clinic have been treated with nicotinic acid. These thirty patients were classified as follows: In ten the asthma was associated with a sinus, bronchial, or pulmonary infection, in three it was due to various inhalants and pollens, in four it was due to a combination of infection plus a sensitivity to inhalants and pollens; in five the asthma was associated with a cardiac deficiency. In the remaining eight asthmatic patients no definite etiologic factors could be ascertained. These patients had been subjected to the usual routine treatment according to indications, such as avoidance of contact with reacting substances and radical sinus surgery. When necessary, they received drugs such as epinephrine, ephedrine, and iodides as well as potassium chloride, histaminase, and histamine. When indicated, they also received dust and pollen desensitization as well as stock and autogenous vaccine therapy. In addition to these procedures, sixteen of the patients in this group had received various forms of intravenous therapy (strontium bromide, sodium bromide, calcium gluconate, and aminophyllin) for acute asthmatic attacks with varying degrees of relief.

In order to study the effect of nicotinic acid on the asthmatic paroxysm, twenty-one patients (Group 1) received intravenous injections of 0.1 Gm. of nicotinic acid (Table I), while nine patients (Group 2), were given only oral treatment (Table II). The oral treatment consisted of doses of 0.2 Gm. of nicotinic acid before meals and on retiring. Supplementary oral therapy to be taken at home was also administered to eighteen of the twenty-one patients who received intravenous therapy (Table III). During the period of treatment no other form of medication was given.

Excellent results obtained by a severe asthmatic patient who followed this therapy is illustrated in Case 5.

From the Adult Allergy Clinic of Mt. Sinai Hospital.

The nicotinic acid for this work was furnished by Endo Products, Inc., Richmond Hill, N. Y.

TABLE I

RESULTS OF INTRAVENOUS INJECTION OF 0.1 GM. OF NICOTINIC ACID ON ASTHMATIC PAROXYSM

CASE NO.	SEX	AGE (YR.)	ASTHMA	TREATED	DIAGNOSIS	NUMBER OF INJECTIONS	AVERAGE TIME RELIEF PER INJECTION
1 (F. R.)	M	58	14 yr.	13 yr.	Infectious asthma and sinusitis	1	8 hr.
2 (A. O.)	M	65	18 yr.	8 yr.	Asthma (Unknown etiology)	1	12 hr.
3 (I. R.)	F	48	28 yr.	7 yr.	Infectious and inhalant asthma and sinusitis	2	10 hr.
4 (E. H.)	F	37	2 mo.	1 mo.	Asthma (Unknown etiology)	3	4 hr.
5 (S. M.)	F	35	8 yr.	8 yr.	Infectious asthma and sinusitis	2	15 hr.
6 (S. S.)	M	68	25 yr.	8 yr.	Asthma and myocardial disease	1	3 hr.
7 (F. B.)	F	35	9 yr.	6 yr.	Infectious asthma and sinusitis	2	4 hr.
8 (Y. B.)	F	38	6 yr.	4 yr.	Infectious asthma, sinusitis, and angioneurotic edema	1	4 hr.
9 (G. S.)	F	40	5 yr.	1 yr.	Asthma (Unknown etiology)	1	5 hr.
10 (I. C.)	M	50	22 yr.	20 yr.	Pollen and inhalant asthma	1	8 hr.
11 (A. U.)	F	41	7 yr.	4 yr.	Infectious asthma and sinusitis	1	12 hr.
12 (M. T.)	M	59	4 mo.	2 mo.	Asthma and myocardial disease	2	10 hr.
13 (M. M.)	F	40	3 yr.	2 yr.	Allergic and infectious asthma and sinusitis	1	12 hr.
14 (L. H.)	F	35	2 yr.	2 yr.	Pollen asthma and hay fever	1	4 hr.
15 (M. A.)	M	67	7 yr.	2 yr.	Asthma and myocardial disease	3	4 hr.
16 (L. L.)	M	42	12 yr.	9 yr.	Pollen asthma and hay fever	1	4 hr.
17 (R. H.)	F	61	27 yr.	13 yr.	Asthma, bronchiectasis, and syphilis	1	Not relieved
18 (R. K.)	F	35	6 yr.	3 yr.	Pollen and inhalant hay fever, asthma, and sinusitis	1	Not relieved
19 (A. M.)	F	31	5 yr.	5 yr.	Pollen and inhalant asthma and sinusitis	1	Not relieved
20 (A. H.)	F	46	1 mo.	1 mo.	Asthma and vasomotor rhinitis (Unknown etiology)	1	Not relieved
21 (H. A.)	M	49	3 yr.	5 yr.	Asthma (Unknown etiology)	1	Not relieved

TABLE II

RESULT OF TREATMENT OF ASTHMATIC PAROXYSM WITH NICOTINIC ACID ORALLY

CASE NO.	SEX	AGE (YR.)	ASTHMA	TREATED	DIAGNOSIS	RESULT
22 (R. S.)	M	57	2 yr.	1 yr.	Asthma, vasomotor rhinitis, and coronary heart disease	Relieved
23 (J. T.)	M	69	6 yr.	5 yr.	Asthma and hypertensive heart disease	Relieved
24 (T. K.)	F	47	3 yr.	2 yr.	Infectious asthma and sinusitis	Relieved
25 (L. S.)	F	38	6 yr.	1 yr.	Asthma (Unknown etiology)	Relieved
26 (T. B.)	F	39	9 yr.	2 yr.	Asthma and vasomotor rhinitis	Relieved
27 (A. B.)	F	57	19 yr.	17 yr.	Infectious asthma and sinusitis	Not relieved
28 (S. B.)	M	47	8 yr.	7 yr.	Infectious asthma and hyperplastic sinusitis	Not relieved
29 (B. C.)	F	41	12 yr.	9 mo.	Asthma and vasomotor rhinitis (Unknown etiology)	Not relieved
30 (E. S.)	F	33	17 yr.	2 yr.	Pollen asthma and hay fever	Not relieved

TABLE III

RESULTS OF ORAL THERAPY WITH NICOTINIC ACID IN PATIENTS RECEIVING INTRAVENOUS THERAPY ALSO

CASE NO.	RESULT
1	Relieved
4	Relieved
5	Relieved
6	Relieved
7	Relieved
8	Relieved
10	Relieved
12	Relieved
13	Relieved
14	Relieved
15	Relieved
2	Not relieved
3	Not relieved
11	Not relieved
16	Not relieved
17	Not relieved
19	Not relieved
21	Not relieved

CASE REPORT

M. S., a Porto Rican married woman 35 years of age, first developed asthma in 1933 following an upper respiratory infection. Except for a chronic bronchitis of two years' duration, her history for allergic diseases both familial and personal was negative.

Examination revealed chronically infected tonsils, a chronic bilateral polypoid ethmoiditis with a deflected septum, and typical asthmatic breathing. Antral washings were negative. A two-plus dust reaction was the only positive intradermal test elicited. At first her treatment was symptomatic but as her asthmatic attacks became more frequent and persistent, a tonsillectomy was performed (1936). No relief ensued. In 1937 antral washings showed slight amounts of pus. In 1938 she was subjected to an antrotomy and a bilateral spheno-ethmoidectomy. No relief was afforded by this extensive operation.

In January, 1941, because of severe attacks of asthma, she was given strontium bromide intravenously. This produced a moderate degree of temporary relief. Strontium bromide orally was ineffectual. When the asthma became increasingly severe in February, 1941, and the antral washings still contained pus, a bilateral Caldwell-Luc operation and a revision of the spheno-ethmoidectomy was performed. In addition, she was injected with an autogenous vaccine prepared from the infected sinuses containing *Staphylococcus albus* and *Staphylococcus aureus* and a non-hemolytic streptococcus. Despite these varying procedures the patient's condition was unimproved and she needed epinephrine injections every four to five hours.

On June 9 she came to the clinic in a severe asthmatic paroxysm. She was given 0.1 Gm. of nicotinic acid intravenously. Within a few minutes her wheezing diminished and the respirations became less labored. Although the patient stated she felt better, there were still scattered rhonchi present. She was given 0.1 Gm. of nicotinic acid to take by mouth every two hours. When seen two days later, she stated that she had not used epinephrine once.

No further treatment with nicotinic acid was given until August 6, when the patient returned to the clinic because of recurrence of attacks. This time she was told to take nicotinic acid orally in doses of 0.2 Gm. before meals and on retiring. The severity of her paroxysms abated, and epinephrine formerly used every few hours was now employed on rare occasions. During the days when she omitted the medication, however, more epinephrine injections were necessary, but, nevertheless, not as frequently as formerly.

On the morning of September 3 the patient awakened with a very severe asthmatic attack, not relieved by epinephrine. At 8 A.M. she received an intravenous injection of 0.48 Gm. of aminophyllin in the emergency room. This partially controlled her asthma until 10 A.M. She was observed in the outpatient department until 11 A.M., at which time it was noted that she was again acutely dyspneic. Nicotinic acid, 0.1 Gm. intravenously, definitely lessened the severity of her asthmatic paroxysm for three hours. Subsequent oral doses of 0.2 Gm. of nicotinic acid completely controlled her asthma, obviating the necessity of epinephrine injections.

After a week, nicotinic acid therapy was discontinued and ephedrine with iodides was substituted. When the patient returned on October 10, she was again taking her usual quota of epinephrine injections. She was advised to resume her oral dose of 0.2 Gm. of nicotinic acid. This was followed by complete cessation of attacks for ten days. When this was discontinued her asthma recurred in all its former intensity. When last seen on November 12, her asthma was completely controlled by oral doses of nicotinic acid.

Analysis of the results obtained in the twenty-one patients (Table I) who received intravenous injections of nicotinic acid for the relief of

asthmatic paroxysms indicates that sixteen, or 76 per cent, were definitely improved from varying periods of three to fifteen hours. Although all the rhonchi in the lungs did not disappear following the administration of nicotinic acid, in most of these patients the degree of subjective relief that ensued was marked.

Of the nine patients (Table II) receiving only oral therapy, five were likewise benefited.

Of the eighteen patients who received intravenous therapy followed by oral therapy, eleven showed decided improvement in their asthma (Table III).

Nicotinic acid orally was therefore efficacious in about 60 per cent of the patients both for the control of acute attacks and for the continuous wheezing.

The clinical manifestations following the administration of nicotinic acid are characterized by a flush and sensation of heat. The flush occurs three to five minutes after an intravenous injection and is confined mainly to the face, neck, chest, and upper arms. The sensation of heat precedes the flush and is of shorter duration. The patients who experienced relief following the appearance of the flush breathe more freely. They often begin to cough and expel tenacious mucous plugs.

DISCUSSION

Nicotinic acid like all other vitamins is remarkably nontoxic. Doses 1,000 times the therapeutic ones have no demonstrable effects in young mice, rats, or dogs.[1] When toxic effects are finally produced, the amounts are so large (2 Gm. per kilogram) that they are quite possibly due to disturbed acid-base relationships. Many thousands of human beings have been treated with large doses with no reports of serious toxic effects, except for an unpleasant flush.[2] Occasionally lassitude, mental depression, palpitation, headache, nausea, vomiting, and dyspnea have been reported. In the group studied, no patient developed any disturbing symptom other than the flush and the drug was well tolerated. What is likewise important is the fact that the efficacy of nicotinic acid was not affected by repeated and continuous use.

The flush produced by nicotinic acid, as already noted, has a latent period of a few minutes. This is possibly due to conversion of nicotinic acid into some other substance or liberation of another substance which is thus activated physiologically. Some workers[2-4] postulate that histamine is liberated. It is difficult, however, for us to see why the liberation of histamine would abort an asthmatic paroxysm.

Large amounts of nicotinic acid orally and intravenously have been shown to have no effect on the metabolism, respiration, or electrocardiogram and but little constant effect on the pulse rate and blood

pressure.[2, 3, 5] While nicotinic acid has very slight effect on the blood flow through the brain,[6] it does increase the blood flow to the upper extremities.[7] It can cause the skin temperature to rise 1.5° C. and remain elevated for thirty to forty-five minutes.[4]

At present we do not know whether nicotinic acid exerts its therapeutic effects by relieving bronchospasm or whether it in some way directly affects the pulmonary vessels. Studies along this line are now in progress. We believe that it is significant that nicotinic acid (intravenously and orally) has a definite physiologic effect on the lungs. We have no reason to believe that a vitamin deficiency exists in the cases treated or that if it did, the relief had any bearing on the therapeutic results obtained.

While nicotinic acid is not offered as a substitute for ephedrine or epinephrine, it is suggested as an adjuvant in the therapeutic armamentarium in the treatment of asthma. It may serve as a substitute when ephedrine is ineffective or when the patient becomes epinephrine fast.

While the group studied is too small for sweeping conclusions, we believe nicotinic acid both orally and intravenously may relieve severe asthmatic paroxysms.

Administered intravenously, 0.1 Gm. of nicotinic acid lessened the severity of the asthmatic paroxysm within three to five minutes in 75 per cent of the patients. The duration of the relief lasted from a few hours up to fifteen hours. When oral therapy was supplemented, freedom from attacks was maintained or attacks became definitely less severe and recurred with less frequency. In our experience, nicotinic acid oral therapy alone, exclusive of any other medication, was beneficial in 60 per cent of the patients who suffered with protracted daily and nocturnal recurring attacks.

SUMMARY

1. Severe asthmatic paroxysms were controlled in sixteen of twenty-one patients by intravenous injection of 0.1 Gm. of nicotinic acid.

2. Relief was obtained within three to five minutes following the injection and seemed to coincide with the appearance of the flush.

3. Of nine chronic asthmatic patients who received 0.2 Gm. doses of nicotinic acid orally, five were benefited.

4. Of eighteen patients who received intravenous therapy, oral therapy also proved effective in eleven patients.

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MILK SENSITIZATION

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MILK is an important atopen in the early years of life. This is well recognized, as is the tendency of milk sensitization to disappear with increasing age, although in many adults eczema, asthma, gastrointestinal disorders, and other ailments may be due to milk sensitivity.

In testing for milk sensitivity many preparations, varying from whole milk to its derivatives, have been recommended. It is probable, however, that most allergists have been disappointed with the results of these tests, for many cases have been encountered in which the skin test for milk was negative, while at the same time either the clinical history or the therapeutic trial definitely incriminated it. McGee[1] concludes that it is the history, and not the skin test, which determines whether or not the person is milk allergic.

Consideration must also be given to the fact that unaltered ingested protein occasionally passes into the milk. It has been demonstrated that the antigen from ragweed, wheat, flaxseed, peanuts, and other substances passes intact into cow's milk.[2] In these cases clinical symptoms are due not to sensitivity to milk but to the unaltered proteins contained in it. Rohrbach[3] in 1925 reported that the clinical symptoms of seven patients, apparently milk sensitive, were relieved when the cows from which they had been obtaining milk were placed upon a changed diet.

Our interest in this subject was particularly aroused by a case of asthma in a young farmer. Clinically he had asthma when he drank milk, and yet his skin tests, made with several different preparations of milk, were negative. He also developed asthma when he handled alfalfa hay. He could milk the cow and suffer no resulting asthmatic attack provided no alfalfa hay was near. An attack of asthma invariably resulted, however, from his drinking milk or being exposed to alfalfa hay.

Skin tests made with an alfalfa extract gave a massive local reaction and brought on a violent attack of asthma. He was then, approximately every other day, given small but gradually increasing doses of a dilute alfalfa extract. At the end of six months, during which time he avoided the use of milk and contact with alfalfa, he was free not only from asthmatic attacks but also from a chronic eczema which had been troubling him. The injections of alfalfa extract were continued twice weekly for the next year, during which time he discovered that he

could drink milk and use other dairy products without resulting asthma. This last season he has been able to harvest his own alfalfa hay without any disturbance. In actuality, this was a case of sensitivity to alfalfa rather than one of milk sensitivity which it at first appeared to be.

In the light of this experience we have, as a matter of routine, done intradermal tests to alfalfa, ensilage, corn, and cottonseed meal along with our milk tests. Among patients so tested were encountered forty whom we believe to be definitely milk sensitive, our opinion being based either upon their history or upon the results of clinical elimination. The skin reactions of these forty patients are shown in Table I. From this table it will be noted that only seven cases (17.5 per cent) gave a skin reaction to milk and that in only one of these was the reaction strongly positive. Of these forty cases, thirty-eight (95 per cent) reacted to alfalfa, four (10 per cent) to ensilage, nine (22.5 per cent) to corn, and four (10 per cent) to cottonseed meal.

TABLE I

SKIN REACTIONS OF FORTY PATIENTS CLINICALLY MILK SENSITIVE

	MILK*	ALFALFA	ENSILAGE	CORN	COTTONSEED MEAL
No. cases positive	7	38	4	9	4
Per cent positive	17.5	95	10	22.5	10

*Only one milk reaction was strongly positive. Two patients reacted to milk and did not react to the other tests.

DISCUSSION

These results suggest that the protein present in the alfalfa hay eaten by cows is likely to pass unaltered into their milk, and in turn, when this milk is ingested, the alfalfa protein contained in it is just as readily absorbed unaltered.

It is also apparent that, of the various proteins which may appear intact in cow's milk, the most common is alfalfa. This suggests that skin tests to alfalfa extract should be routine and that a positive reaction incriminates milk produced by cows fed with alfalfa.

Although our experience is too limited for us to make any definite statements, we would suggest that desensitization to alfalfa might be of value in certain allergic ailments which are apparently due to milk.

In milk-sensitive cases, changing from the use of cow's milk to goat's milk has not been entirely satisfactory.[4] As a result many clinicians eliminate milk entirely and substitute soy bean preparations. This has many disadvantages which, it is suggested, might be obviated by the use of milk obtained from animals which are not fed alfalfa.

CONCLUSIONS

1. It is apparent that some cases of so-called sensitivity to cow's milk are in actuality due to a sensitivity to alfalfa.

2. Routine testing with an alfalfa extract is recommended, and a positive reaction to this test would incriminate milk obtained from animals fed alfalfa hay.

3. Many clinical disappointments at changing from cow's milk to goat's milk are due to the fact that goats are also fed alfalfa.

4. Many cases of so-called milk sensitivity can be corrected by desensitizing to alfalfa.

5. It is re-emphasized that probably the simplest method of obtaining a nonallergic milk would be to get it from animals whose diet does not include certain disturbing substances among which alfalfa is the most frequent offender.

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VITAMIN D IN VERNAL CATARRH

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VERNAL catarrh is believed to be an allergic condition. It has been found associated with axial myopia and keratoconus. In both of these eye lesions, systemic allergic phenomena have been observed frequently. In previous reports I have shown that axial myopia and keratoconus actually may be reduced by the administration of vitamin D and calcium.[1] Furthermore, some investigators have claimed that there is an underlying calcium deficiency in vernal catarrh. Basing the treatment on experience, vitamin D and calcium were prescribed for a series of patients suffering from this condition.

Forty-seven consecutive patients were studied from June, 1937, to December, 1938. Their ages ranged from 11 to 76 years. Their symptoms varied from mild to very severe and almost unbearable. All of them had definite, subjective complaints. Itching, worse in hot, humid weather, was the most frequent symptom. Sensitiveness to light, matter in the eyes, and excessive tears also were causes for complaint. The conjunctivae had a basic, milky appearance with a blue sheen and were acutely injected. A stringy or rubbery discharge was present in every case. Eleven suffered from the palpebral type, while thirty-six had the bulbar. In the former there were gradations from the almost smooth conjunctiva to the "cobblestone" plaque variety, while in the latter the gelatinous overgrowth of the limbus sometimes was definite, even marked, but more often it resembled the normal limbus. Eosinophilia was infrequent in the conjunctival smears. Twenty-two of the patients gave a previous history of the same seasonal complaints. Eight, including six of the bulbar type and two of the palpebral, had symptoms persisting throughout the four seasons.

To evaluate the method of therapy, several other well-known forms of treatment first were tried. Fourteen consecutive patients had their lids swabbed twice weekly with 1 per cent silver. They received a prescription for a 1:500 zinc solution and were directed to place one drop in each eye three times daily. Six others received similar therapy, except that the zinc solution was fortified with 1:1000 adrenalin chloride. Nine were asked to irrigate their eyes with an eye cup six times a day, using a solution of boric acid and bicarbonate of soda, a teaspoonful of each to two glasses of water. In the first group, three mild cases had no further subjective symptoms. Four were improved and seven showed

Read before the Clinical Society of the New York Eye and Ear Infirmary.

no improvement. Those in the second group who received silver and zinc drops with adrenalin generally felt better. In one mild case there were no further complaints. Four others were improved. After early improvement in the sixth, the patient again suffered as originally. The nine who irrigated their eyes all had some relief. None of these several groups showed any objective improvement.

After these patients had been under treatment for from two to four weeks, the twenty-five not entirely relieved, together with the remaining eighteen, received vitamin D in the form of viosterol* and calcium in the form of mineral mixture tablets.† Dosage of the latter was gauged by the milk intake. If a patient drank one quart of milk daily, one tablet was prescribed. For each glass less than a quart, two tablets were added. The calcium was taken before breakfast because it is best absorbed in an acid medium. As a matter of routine, 60 drops of viosterol were given after the meal. No other change was made in diet or regimen. No local therapy was applied during this particular study.

This large group had been under observation from one to eighteen months, the average time being four months. In all but one patient there was definite and usually decided improvement. This improvement, as a rule, became manifest in seven to fourteen days. In one patient with the severe "cobblestone" type, no relief was felt until six weeks had elapsed, after which he improved considerably for the remaining two months of the summer.

The amount of benefit to each patient varied. Eleven were completely relieved of any subjective symptoms; thirty showed marked improvement with only occasional itching, or a slight discharge, worse in the morning. Photophobia and lachrymation were much diminished. The twenty-five patients who primarily had received other treatment all felt that their improvement was far greater with vitamin D and calcium.

Objectively, too, improvement was recognizable. Blepharospasm decreased to a great extent and even disappeared in some cases. Diminution of conjunctival congestion always was noticed with subjective improvement. But, even with those patients from whom there were no further complaints, the conjunctivae remained mildly injected. The milky appearance was lost in many cases. The stringy discharge was not seen in nine, while the rest showed it to a less degree. Conjunctival smears from four patients who formerly showed an eosinophilia now revealed normal findings.

The one who showed no improvement was a woman 59 years of age, who complained of itching of the eyes, with photophobia and lachrymation. There was a little stringy discharge and barely perceptible overgrowth of the limbus; the conjunctivae were mildly injected. Hers was a mild case. Despite increased dosage of viosterol, up to 200 drops

*Each gram of viosterol contains not less than 10,000 vitamin D units (U.S.P.).

†The mineral mixture tablet contains the following in milligrams: calcium, 140; phosphorus, 83; iron, 1; copper, 0.05; magnesium, 2.8; sodium, 5; potassium, 5.

daily, and administration of 60 c.c. of dilute hydrochloric acid before the calcium tablets, she remained unimproved.

Five of the seven patients who were seen the following spring and summer were free from symptoms.

In three of the cases studied, there was only negligible to slight improvement noticed after six weeks of the prescribed treatment. The patients still complained of itching, discharge, and photophobia. Since it was known from previous experience with myopia that larger vitamin D dosage might prove of further value, the viosterol was increased to 125 drops daily. On the next visit of the patients, in two weeks, definite improvement was noted, with complete relief in one case. For the other two, 200 drops daily were prescribed. Their symptoms then disappeared, and they were kept on this dosage.

Toxicity from vitamin D as utilized in this work is to be expected only rarely. Sixty drops of viosterol, equivalent to 13,860 units, is a comparatively small dose, when it is realized that as much as 500,000 units daily are given to arthritics. Mild symptoms, however, were present. Two patients developed a slight erythematous rash, one a mild papular eruption, and two complained of regurgitation. Temporary discontinuance of the oil promptly cleared up these complications. The ocular fundi remained essentially the same. Those patients manifesting arteriosclerosis showed no advancement and those who were free from sclerosis did not develop it. Urinalyses were negative.

Because hypertrophy of the thymus has been mentioned in association with vernal catarrh, three patients, two with the severe, follicular palpebral type, the other with the mild bulbar, had roentgenograms taken of their chests. None of them showed the presence of the hypertrophy.

Examination of the fundi, checked with fields and blind spots, revealed the presence of retrobulbar neuritis in six cases. Foci of infection were investigated and treated at the same time that the patients received their vitamin therapy, so no definite conclusions could be drawn from the improvement and cures. Two young girls with moderate facial acne showed completely clear skins after being under treatment for seven weeks.

In nine cases, the therapy was studied further by discontinuance for one to three weeks. All nine complained of the return of their initial symptoms. In each instance, relief was obtained again through the administration of vitamin D and calcium.

It may be well to mention that three patients of this series presented clinical evidence of early vitamin A deficiency. A mild xerosis of the conjunctiva was observed. Treatment for these cases was changed to include vitamin A. Oleum percomorpheum* was prescribed, the same number of drops being given as with the viosterol. Within a ten-day period the xerosis cleared up in all three.

*Each gram of oleum percomorpheum contains not less than 60,000 vitamin A units (U.S.P.) and not less than 8,500 vitamin D units (U.S.P.).

CONCLUSION

1. In a series of forty-seven consecutive cases of vernal catarrh, forty-three received vitamin D, in the form of viosterol, and calcium in the form of mineral mixture tablets.

2. The patients represented the various types of vernal catarrh.

3. Forty-two of the forty-three showed definite improvement.

4. This improvement in twenty-five cases was found to be superior to that effected through several other accepted therapeutic procedures.

5. These results suggest a disturbance of the vitamin D-calcium-phosphorus metabolism in vernal catarrh.

6. For the treatment of this catarrh, the administration of vitamin D and calcium has proved to be of real value.

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35 E. 64TH STREET

THE POLLEN CONTENT OF THE AIR IN BELO HORIZONTE, BRAZIL

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FOLLOWING the example of what Durham[1-3] and others have done in the United States, we undertook, in January, 1940, a study of the pollen content of the atmosphere of various cities in Minas Gerais, a state in the central part of Brazil. So far, this study is the only one carried on in Brazil and one of the first in South America.

It is a general impression among doctors in Brazil that cases of hay fever do not occur in this country, but no one has ever undertaken a study to ascertain if such belief is right or if some cases of pollinosis have been confused with other disease. If hay fever does not occur here in Brazil, it would be interesting to investigate the reason why it is so. We proposed to investigate the problem of hay fever in Brazil on an accurate basis not yet tried by anyone in this country.

The present paper reports only our findings of the daily tests of the pollen content of the air of Belo Horizonte and surroundings, from January, 1940, up to July 15, 1941. The clinical aspect of the subject will be discussed in a later communication.

METHOD

Daily slides coated with glycerin jelly and methyl green were exposed for twenty-four hours. The counting of the pollen grains was made by ourselves and the number found recorded per 1.8 sq. cm. We adopted this unit area to provide a means of comparison with the counting made by most foreign investigators. We secured from the Weather Bureau of Minas Gerais data of the variation of temperature, rain, and wind. At the present time we are extending our study to other cities of the country, through the cooperation of colleagues who expose the slides in their cities, for example, in Rio de Janeiro, São Paulo, and others. This nationwide survey we hope to get next year.

RESULTS

There is in our region of study only one season of pollination—that of the grasses—which occurs in the last two weeks of May and the first of June (Figs. 1 and 2). The 1940 season was somewhat longer, from May 16 to June 12.

The grass pollens found were attributed principally to *Cynodon dactylon* which is a grass extensively distributed in our region. We

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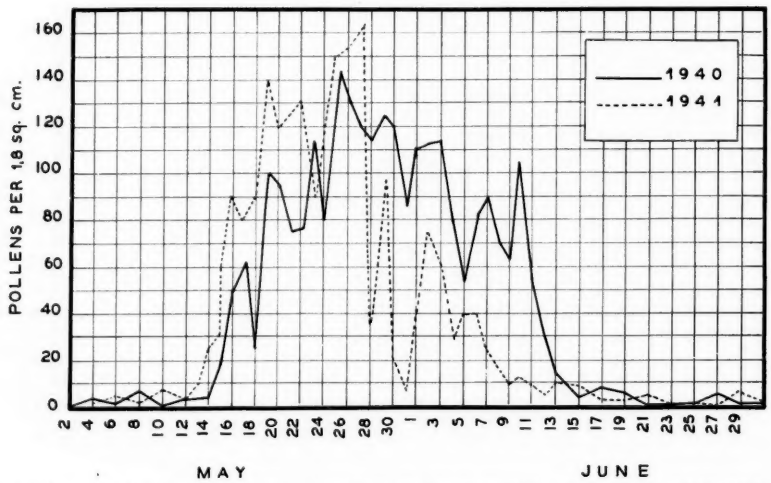

Fig. 1.—Graph showing the daily counting of grass pollens during the 1940 and 1941 seasons.

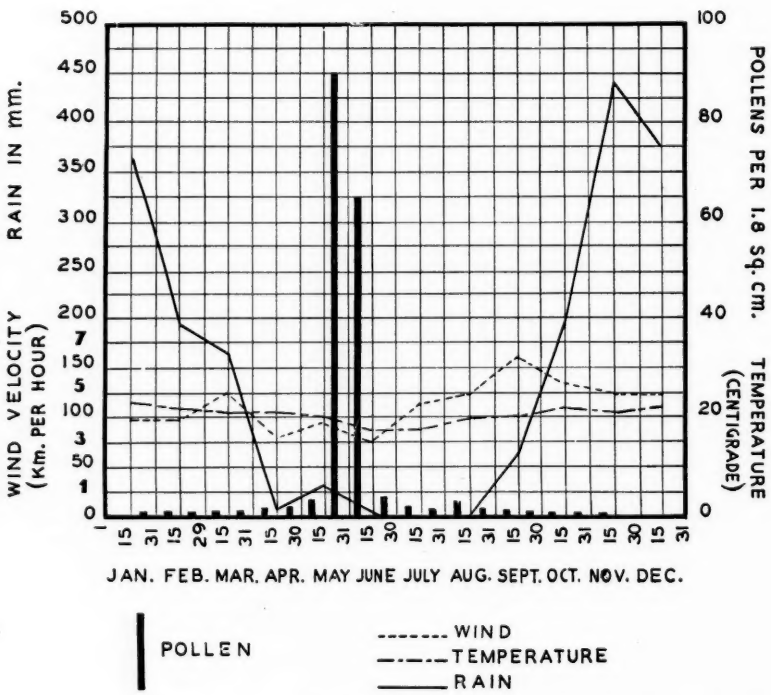

Fig. 2.—Graph showing the monthly fluctuations of pollen counting, rain, wind velocity, and temperature, in 1940. All figures represent the average of each month.

could observe that this grass was flowering profusely during the high pollen counting. Besides *Cynodon dactylon* of course many other grasses may be seen in our section, as for instance *Melinis minutiflora* which is extensively planted for pasture. However we did not ascertain from which grasses the pollens were counted.

Among the other pollen-producing plants of importance in allergy, we have only one kind of ambrosia (*Ambrosia polystachya*). It is sparsely distributed and its pollen was not seen in the exposed slides. The pollen of the chenopod-amaranth group could be observed from time to time in the slides but in insignificant amount without showing a definite season of pollination. This holds true in reference to tree pollens.

The hay fever problem in our region of study seems to be much simpler than that of the United States, especially because of the lack of a ragweed pollination season.

SUMMARY

1. Daily tests of the pollen content of Belo Horizonte, Brazil, were were made from January, 1940, to July, 1941.

2. Only one pollination season occurs in the region studied—that of grasses—which lasts from the end of May to the beginning of June.

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MECHOLYL DESENSITIZATION IN THE TREATMENT OF ASTHMA

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BRONCHOSPASM is dependent upon impulses transmitted by the vagus nerve, a division of the parasympathetic nervous system. These cholinergic fibers presumably liberate a chemical mediator, acetylcholine, when stimulated. It is thought that acetylcholine is destroyed immediately in the body by the activity of an enzyme, cholinesterase. Mecholyl or acetyl-beta-methyl-choline-chloride is a stable derivative of acetylcholine and, when introduced into the body of an allergic person, may produce an attack which is clinically indistinct from asthma. Moll[2] administered this drug to twenty-eight asthmatic patients, and in almost every instance an attack of asthma ensued. A series of nineteen control subjects showed general signs of cholinergic stimulation, such as flushing, sweating, lacrimation, and salivation, but did not develop wheezing in the chest. Moll concluded that the peculiar tropism of choline for the bronchial system appears to be due, not to a state of increased sensitivity of the whole parasympathetic system but only of the bronchial nerve endings, or the bronchial muscle itself. He believed, moreover, that lung damage is an essential factor in determining the abnormal bronchial response.

Pearson[1] desensitized seven persons who were sensitive to wheat by giving increasing doses of mecholyl over a period of twenty to sixty days. In this series there were four cases of asthma, two cases of angioneurotic edema, and one case of eczema. The drug was administered during a controlled symptom-free period when wheat was withdrawn from the diet. In each case, when wheat was restored to the diet, the original symptoms did not recur, and the patients remained well for a year. Pearson concluded that mecholyl was of value in those cases in which a specific antigen could be found and eliminated during the period of treatment. He felt that allergies of a continuous nature were usually made worse by the treatment.

The study presented was an attempt to build up a tolerance to mecholyl, or to increase the production of cholinesterase in an unselected group of chronic asthmatic patients. A control group of asthmatic patients were given physiologic saline solution. No attempt was made

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Presented before the American Federation for Clinical Research, Atlantic City, May, 1941.

to eliminate any antigens or to control the environmental factors in any way. The subjects were all clinic patients and received daily injections except on Sunday.

The initial dose was 0.5 mg. given hypodermatically, as it was found that larger doses precipitated an attack of asthma. Fresh solutions were used weekly, as it was found that the potency diminished over longer periods of time. Frequently attacks occurred when the same dose of a fresh preparation was given.

The subjective response usually shown was a feeling of flushing, lacrimation, and profuse watery nasal discharge, particularly in those with vasomotor rhinitis. The effects were felt in a few minutes and were usually of short duration, clearing up within ten to thirty minutes. It was frequently necessary to give atropine to terminate attacks of asthma which had been precipitated by the mecholyl. Tolerance to the drug developed very slowly, and it was never possible to increase the dose above 6.5 mg. without reactions. The average tolerance dose which was established during the period of observation was about 5 mg. In Pearson's series, four patients tolerated 5 mg., two patients, 3 mg., and one patient, 10 mg., which corresponds fairly well with the present group.

Twenty-four patients with chronic asthma having attacks from one to ten times weekly were treated. One patient was never free from wheezing throughout the course of treatment. Five patients had a concomitant vasomotor rhinitis. Seven patients received fewer than ten injections, and these cases were discarded. Seventeen patients received ten or more injections, the average number of treatments being twenty-eight. One subject received sixty-two injections. Of the seventeen patients, eleven received mecholyl and six received saline. In no case was the improvement marked. Moderate relief as to the frequency and severity of attacks was experienced by six patients, or 54.5 per cent, of the mecholyl series and by four, or 66.6 per cent, of the saline series. Conversely, five patients, or 45.5 per cent, of the mecholyl series obtained no relief, and two of these were made worse. Of those who received saline, two patients, or 33.4 per cent, received no benefit. Thus again is brought out the fact that anything that is done for asthmatic patients may be followed by some improvement. The conclusions drawn from this study are that mecholyl is of no material benefit in hyposensitization treatments of chronic asthmatic patients.

SUMMARY

1. Twenty-four patients with chronic asthma were studied.

2. These cases were divided into two groups. One group received increasing doses of mecholyl daily, and the other group, serving as a control, received saline solution. Of the seventeen patients who were given ten or more injections, eleven received mecholyl, and six saline.

3. Fifty-four per cent of the mecholyl treated cases reported improvement, whereas, 66 per cent of the saline series were improved. It is concluded that mecholyl is of little value in the hyposensitization treatment of asthma.

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Special Reports

CONTACT DERMATITIS FROM EXPOSURE TO DYES

Case Report

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Schwartz and Tulipan[1] have cited the combined statistics of the Labor Commissions of New York and Ohio which showed in 1934 that of about 1,600 cases of occupational dermatitis, forty-five were attributed to dyed fabrics. Dermatitis has been reported to be caused by dyed dresses, socks, dress shields, and collars made of silk, rayon, cotton, and wool. Simon and Rackemann[2] reported dermatitis due to wool dyed with the anthracene-alizarin-chromate group of dyes. They cited a case of dermatitis in a man 29 years of age from dyes in socks, a blue serge suit, an overcoat collar, a hat band, garters, upholstery, and furniture. Patch tests were positive to several dyes and to dyed cloth. Trouble first started with an abrasion on the wrist from a stiff cuff. The hands, forearms, and neck were affected, and later the face, eyelids, and genitals became involved, probably from the transfer of the dye by the hands to these areas. Kling[3] reported cases due to aniline, orthotoluidine, and black setacyl R. Bonnevie and Genner[4] reported fifteen cases of dermatitis from dyed clothing. The azo dyes gave positive reactions to patch tests, three triphenylmethane dyes gave weak positive reactions, and all the other dyes were negative. These studies lead the authors to suspect that the azo linkage of the dyes was the irritating property. Killeck and Ingram[5] discussed dermatitis from dyed fabrics, stating that paraphenylendiamine is the most important dye. Various dyes used are derived from aminodiamines, aminophenols, diphenols, and their substitutes.

Despite the fact that many fabrics are dyed, only a small percentage of wearers are affected. Tests in suspected individuals should be performed with the raw fabric, the finished dyed fabric, and individual dyes used in the manufacture of the finished article. Before incriminating the dyes, positive reactions to patch tests should be obtained not only with finished fabrics themselves, but also with the actual dye.

CASE REPORT

J. A., white male, married, aged 42 years, bakery truck driver for eight years, was first seen on Jan. 14, 1940, at which time he complained of swelling, itching, and redness of the entire face, both hands, forearms, and left leg. He gave no past personal or family history of any allergic manifestation. On March 28, 1936,

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while driving a truck, he was in an accident and sustained compound fractures of the left tibia and fibula with a complicating gas gangrene involving the left leg. He was confined to the hospital for about one year because of an osteomyelitis of the tibia and fibula and cellulitis of the leg. At the time of discharge from the hospital, the left leg was still infected and required a drain. He was treated by his physician at home for several months. As one of the forms of treatment, scarlet red ointment was applied daily to the leg wound for about one week. At the end of that time he suddenly developed a marked swelling of the entire left leg, accompanied by redness, itching, and swelling; also redness and itching of the face, both hands, and lower forearms. Application of scarlet red was immediately discontinued, but the lesions of both hands, forearms, and left leg persisted for six weeks. No further skin lesions appeared for one year, although a purulent discharge from the left leg was continuously present. Another physician was consulted and scarlet red ointment was again applied. Within one hour, swelling, redness, and intense itching recurred, involving the entire left leg, face, and hands. The lesions were present for about one month. From about July, 1938, to February, 1939, no skin manifestations occurred, although the leg was still infected. In February, 1939, the swelling, redness, and itching of the face and hands recurred. At this time both legs and the lower and upper parts of both forearms were involved. There was no history of scarlet red application at this time. The above complaints were present continuously from February, 1939, to January, 1940. No relief was obtained from calamine lotion or bran and bicarbonate of soda baths.

Physical examination was essentially negative except for the appearance of the affected parts. Swelling and redness involved the entire face, both hands, forearms, and legs. Over these areas could be seen many vesicles and crusts. Some of the areas had become thickened, scaly, and fissured. A purulent discharge exuded from the lower outer aspect of the left leg.

The blood differential count showed no eosinophiles. The blood Wassermann, Kline, and Hinton tests were negative. The blood chemistry, bleeding time, platelet count, and urine were also negative.

Patch testing with thirty standard eczematogenous substances gave the following positive reactions: scarlet red ointment, 3 per cent; paraphenylendiamine, 2 per cent; and aqueous solution of methyl orange, 5 per cent. Further patch testing with clothing material worn by the patient produced positive reactions to the following: brown sweater, gray sweater, brown overcoat, brown pants, blue pants, and red pajamas. Patch testing to silk, rayon, cotton, and wool and their allergenic oils gave negative tests.

The positive patch test to scarlet red ointment appeared one-half an hour after its application and was accompanied by marked swelling, redness and itching of the face, both hands, wrists, forearms, and legs.

On March 22, 1940, the patient's home was repainted and he developed a marked exacerbation of swelling, redness, and itching of the face, neck, hands, forearms, and legs. Patch testing was done with the white paint and varnish. The test to white paint was negative. Varnish produced a markedly positive local reaction in about one hour and was accompanied by marked swelling, redness, scaling and itching of the face, neck, chest, abdomen, and hands. Treatment consisted of a course of x-ray treatments, histamine therapy, and avoidance of contact with dyed clothing and paints. The skin lesions have completely disappeared and have remained so from mid-April, 1940, up to the present time.

SUMMARY

A case of contact dermatitis to scarlet red and to dyed fabrics is presented.

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A CASE OF SEVERE ALLERGY TO PEA

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FOOD allergy[1] has been known for centuries. In the adult it is relatively infrequent. Stuart and Farnham[2] found that the greatest incidence of food sensitiveness was encountered in the second year of life. Thereafter, there was a rapid decline until the eighth year, when it became negligible. Severe allergy to certain foods, such as egg, milk, buckwheat, nuts, legumes, and cabbage, has been observed. Starck[3] described the case of a 2-year-old child who died as a result of being fed a few spoonfuls of pea porridge. Feinberg and Aries[4] described a case of severe asthma from inhalation of the vapor from peas which were being cooked. Intradermal tests with pea extract were positive in a dilution of 1:10,000,000, and passive transfer tests were positive in a 1:10,000 dilution. A dish of Coca's solution was exposed to vapor 5 feet from a pot of peas which were being cooked, and passive transfer tests with this were found to be positive. Pagniez and Lieutand[5] reported the first case of so-called epilepsy in a young adult whose seizures were precipitated by the ingestion of chocolate. Since their publication other cases of convulsive seizures definitely allergic in nature have been reported. Coca and Grove[6] carried out immunologic studies on a patient who developed asthma and gastrointestinal symptoms upon consuming green peas, and they demonstrated that the causative allergic factor was a protein. Tryptic digestion of a fraction of pea extract resulted in a diminution of the atopic activity which corresponded with a loss of protein by digestion with the enzyme.

The following case of food allergy we feel is worthy of reporting.

CASE REPORT

A. A., a white male, aged 24 years, was admitted to the Medical Service, Letterman General Hospital, April 18, 1941, complaining of sore throat, fatigue, vertigo, chills, and fever of two days' duration.

Family History.—The father had been separated from the family for years, and no information concerning his health was obtained. The mother was living and well. There were four siblings and two half-brothers living and well. There was no history of allergy in the family.

Personal History.—He had been employed in a lumber mill before induction into the army. Past illnesses comprised measles in childhood and fracture of the wrist in 1938. He had a tonsillectomy in 1923 and an appendectomy in 1938. There was a history of hay fever during the summer months in northern California since 1935.

Physical Examination.—The temperature was 100.8° F.; pulse, 104; respiration, 22; blood pressure, 136/70. The physical examination was essentially negative except for an injected pharynx.

From the Letterman General Hospital, Presidio of San Francisco.

Laboratory Findings.—W.B.C. was 19,200; R.B.C. 6,000,000; Hb., 90 per cent. Differential count was normal (2 per cent eosinophiles); three additional differential counts were normal. Chest plate showed pneumonitis (left base). Urine was normal. Nasal smear showed no eosinophiles.

Course in Hospital.—The admission diagnosis was an upper respiratory infection, and a chest plate revealed pneumonitis of the left base. He was started on supportive treatment with fluids and cough sedatives (elixir terpin hydrate). The day following admission, he consumed 3 to 4 spoonfuls of soup containing dumplings, tomatoes, peas, beans, and carrots and within a few minutes experienced nausea and a desire to urinate and defecate. He hurried to the latrine, vomited forcefully, was dizzy and weak, and collapsed. He was carried to bed by other patients, and the ward officer was called immediately. Examination revealed that he was acutely ill, breathing with stertorous shallow gasps, cyanotic, and pulseless. His skin was cold and clammy, and his body was rigid. Urination was involuntary. After he was in bed the skin was noted to be deeply flushed except for the fingers and toes which remained cyanotic; the respirations became deep and labored, and the pulse became perceptible. Within a few minutes he opened his eyes and talked but was confused. He complained of a sensation of constriction in his chest, vertigo, and numbness of the extremities. The blood pressure was 92/60; the pharynx and uvula were edematous; the chest was clear. He was given adrenalin, and the cyanosis, flushing of the skin, and dyspnea became less marked. About an hour later he was able to give a history of the events leading to his collapse.

He admitted that, since the age of 6 years, he had had similar attacks which lasted from a few minutes to two hours after the ingestion of peas or beans (kidney or Lima), especially peas. These foods would produce a feeling of constriction in the throat and chest if he was present when they were cooking. Accordingly, a diagnosis of food allergy was made, and allergy studies were carried out.

Skin Tests.—He showed severe reactions (4+) to green pea (0.001 mg. N) which by scratch test produced a large urticarial wheal with pseudopods and erythema (extract was prepared by Army Medical Center, Washington, D. C.); marked reactions (3+) to spring mixture (brome, Bermuda, red top, rye) dilution 1:33⅓, fall mixture (pigweed, western ragweed, coast sage, spearscale) dilution 1:33⅓, and tree mixture 1:100; and moderate reactions (2+) to corn, shell fish, onions, spinach.

Positive Passive Transfer Tests.—Pea gave severe reaction (4+); spring mixture, marked reaction (3+); fall mixture, marked reaction (3+).

One week after admission the patient had a recurrence of an upper respiratory infection, sore throat, cough, and fever (104° F.) which responded well to sulfathiazole, potassium iodide, and gargles.

Three weeks after admission he again unknowingly consumed a few spoonfuls of soup containing peas and experienced a slight constriction in his chest and throat and flushing of the skin. One month later a similar experience occurred with the identical symptoms. Neither of these attacks required any medication for relief.

His course in the hospital was otherwise uneventful and he was discharged from the Army for disability.

DISCUSSION

The clinical history and the severe skin sensitivity obviously justify a diagnosis of food allergy. The failure to confirm by skin tests or passive transfer the clinical history of sensitivity to beans warrants explanation, since both foods are members of the legume family.

Vaughan and Wilson[7] formulated a botanical classification of foods for use in the diagnosis of food allergy and pointed out that a relationship existed between peas, beans, peanuts, soybeans, clove, and alfalfa, the similarity being due, apparently, to identical globulins. Piness and his co-workers,[8] on the other hand, after statistical analysis of the value of this botanical classification, found the method unreliable in predicting skin or clinical sensitivity when the reactions to a botanically related food were known. Levine and Coca[9] expressed the opinion that passive transfer reactions, when positive, paralleled the true skin tests. Fineman and Peshkin[10] concluded that passive transfer is not as satisfactory as skin testing for determining sensitivity. Withers[11] demonstrated that passive transfer tests, as in the case of skin tests, do not in any way indicate the degree of clinical sensitivity or reacting time of the food tested, and he cited the case of a patient who exhibited a questionable positive passive transfer test to peas and a strongly positive test to beans; however, clinically, a small amount of peas produced marked symptoms while a large amount of beans was well tolerated. The failure to obtain positive skin tests in clinically hypersensitive patients may be accounted for on the basis that the atopen used for testing does not represent the form which is harmful to the patient.[12] The atopen in the raw state may be well tolerated; nevertheless, the patient may be sensitive to this when cooked; therefore, the possibility of sensitivity to the split products of digestion must be considered.

The clinical history of sneezing, coryza, and lacrimation during the spring season together with the positive skin reactions and passive transfer tests with the grasses and weeds justify a diagnosis of pollenosis and confirm the observation that gastrointestinal allergy in the majority of cases occurs in conjunction with other allergic syndromes.

SUMMARY

1. A case of extreme allergy to green peas has been presented.

2. The failure to confirm the clinical history of sensitivity to beans has been discussed.

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Selected Abstracts

Asthma and Hay Fever

UNDER THE DIRECTION OF SAMUEL M. FEINBERG, M.D., AND
THEODORE T. BERNSTEIN, M.D., CHICAGO

The Use of Dilantin Sodium in Bronchial Asthma. Shulman, M. H.: New England J. Med. **226**: 260, 1942.

The author advocates using dilantin sodium in bronchial asthma in children. His reasoning is based on a consideration of the psychogenic aspect of bronchial asthma and on the fact that the drug is used as an anticonvulsant in epilepsy. Seven cases of intractable severe bronchial asthma were selected for treatment. These children were found by skin tests to be sensitive to many allergens. The medication was carried on for a period of five months or longer. Dosage was determined for each patient individually, and the average dose was found to be 1½ to 3 gr. daily and is given continuously to prevent asthmatic attacks. With adequate dosage, six of the patients remained constantly free from attacks of bronchial asthma. The medication worked well in controlling asthmatic attacks brought on by emotional upsets and other psychogenic factors, but in two cases complicated by seasonal allergies, the seasonal allergic symptoms could not be controlled with dilantin sodium. Those patients with personality changes became much brighter mentally. In two cases, a stubborn eczema which had persisted since infancy cleared while the medication was being taken.

A Method of Determining the Probability of Constitutional Reactions During Treatment of the Ragweed Hay Fever Patient. Sherman, W. B., and Hebald, S.: Am. J. M. Sc. **203**: 383, 1942.

The authors had previously prepared two main antigenic fractions from ragweed pollen extract by fractional precipitation with ammonium sulfate at pH 4. Practically all hay fever patients tested reacted to Fraction 1, some were equally sensitive to Fraction 2, and others reacted very little or not at all to this second fraction. Studies had also shown that most patients under treatment developed blocking antibodies for one antigen (Fraction 1) and only a few developed the blocking antibody for the second antigen (Fraction 2).

A group of 221 ragweed hay fever patients was tested with both fractions intracutaneously. Only 14 per cent of the patients who gave larger reactions to Fraction 1 than to Fraction 2 had constitutional reactions under treatment (thirteen of ninety-three cases), whereas 80 per cent of the patients whose reactions were greater to Fraction 2 than to Fraction 1 had general reactions (sixteen of twenty cases). Of 108 patients whose reactions to Fraction 1 and Fraction 2 were equal, eighty-one, or 75 per cent, had constitutional reactions. When 214 cases were tested with Fraction 2 and the results computed upon the basis of the size of the reactions obtained, it was found that seventy-nine patients reacted slightly or not at all, and of these 10, or 13 per cent, had constitutional reactions. Of sixty-four patients who reacted moderately, thirty-four, or 53 per cent, had general reactions; of seventy-one patients whose reactions were marked, sixty-two, or 87 per cent, had reactions. Passive transfer tests showed similar results.

Intracutaneous tests with Fraction 2 on hay fever patients might be helpful in determining in advance which patients are apt to have constitutional reactions and should be treated cautiously.

Electrophoretic and Ultracentrifugal Analysis of Hay-Fever-Producing Component of Ragweed Pollen Extract. Abramson, H. A., Moore, D. H., and Gettner, H. H.: J. Physical Chem. **46**: 192, 1942.

The authors present data on the electrophoretic analysis, the sedimentation constants, and the diffusion constants of some of the electrophoretically homogeneous allergenic constituents of giant and dwarf ragweed pollen. These components are colorless, negatively charged, and highly skin reactive and produce hay fever and asthma. They exhibit the property of slow mobility, and when ultracentrifuged at about 150,000 times gravity, a sedimentation constant that is low and smaller than the smallest sedimentation constant given in Swedberg and Pedersen's table of proteins. This unpigmented fraction also diffuses rapidly as compared with proteins like serum albumin. The above properties indicate this component has a low molecular weight, which is calculated by the authors to be about 5,000. On the basis of chemical reactions with different protein precipitants, they believe the molecule is proteinlike in character, possibly a polypeptide. The low value of the molecular weight fits in with the fact that the active material is easily introduced into the skin by electrophoresis. In addition to the major unpigmented fraction, electrophoretic studies also indicate the presence of four to six minor pigmented components, which migrate fast and are skin reactive. Preliminary experiments with timothy grass extract indicate the presence of a major unpigmented and several minor pigmented components, all of which have the properties of the corresponding components found in the ragweed extracts.

Electrophoretic Skin Studies. I. Reaction to Common Grasses. Shilkret, H. H.: J. Invest. Dermat. **5**: 11, 1942.

Five persons, four of whom were clinically sensitive to grass pollen, were found to give positive skin reactions to extracts of timothy, orchard grass, sweet vernal grass, June grass, and red top when these extracts were introduced into the skin by electrophoresis. These skin reactions, in general, are parallel to those reactions produced by the same extracts with the scratch or intradermal technique.

Results in the Treatment of Hay Fever. A Comparison of the Results of Preseasonal and Perennial Methods of Treatment of Ragweed Hay Fever. Markow, H., and Rosen, E. A.: M. Rec. **155**: 203, 1942.

This study is a report of 188 cases of ragweed hay fever treated in 1940 and included only patients who were receiving their third or more consecutive year of treatment. The perennially treated group was composed of 118 patients, 87 per cent of whom had had satisfactory results from treatment, while the preseasonally treated group, which consisted of 70 persons, showed a satisfactory result in 77 per cent. A further analysis of these patients, based upon the number of years each patient had received treatment prior to the 1940 season, showed that in those patients receiving their third to eighth consecutive year of treatment, the perennial method yielded results superior to the preseasonal method. The patients who had received nine or more years of treatment by 1940 showed equally good results with both methods of treatment. However, the number of patients in this group was small.

Immunology

UNDER THE DIRECTION OF MATTHEW WALZER, M.D., AND
MURRAY ALBERT, M.D., BROOKLYN

Experimental Evidence for Histamine Release in Allergy. Katz, G., and Cohen, S.: J. A. M. A. **117**: 1782, 1941.

The writers investigated the role played by histamine in allergic reactions in humans. It had previously been demonstrated that blood cells of sensitized animals released part of their histamine content into the plasma when mixed in vitro with the related antigen. The quantity of histamine released was proportional to the degree of sensitivity.

In the present experiments venous blood obtained from allergic individuals with circulating atopic reagins was incubated with the specifically related allergen. Plasma histamine determinations were made before and after incubation. An increase in the plasma histamine was observed following incubation of whole blood with the specifically related allergen. Since incubation of plasma alone with the allergen failed to produce a rise in histamine level, the cells were considered to be the source of the increased plasma histamine. The rise in plasma histamine seemed to parallel the degree of clinical sensitivity of the patient rather than the degree of the cutaneous reaction. There was some evidence to indicate that histamine is not the only active substance which is released during the antigen-antibody reaction.

Reversed Passive Skin Sensitization to Horse Serum in Human Beings. Wright, G. P., and Hopkins, S. J.: J. Path. & Bact. **53**: 243, 1941.

The intracutaneous injection of 0.1 ml. of a serum taken from a horse serum-sensitive individual into skin sites injected twenty-four to forty-eight hours previously with 0.1 ml. of horse serum (tetanus antitoxin) resulted in a positive skin reaction. Normal human serum failed to produce similar reactions. The reversed passive skin reaction occurred with the antiserum in dilutions as high as 1:625. As early as one-half hour after the skin had been injected with horse serum, it was possible to elicit a positive reaction by injecting the human antiserum. If a number of hours were permitted to elapse, the antiserum produced a much greater reaction. A comparison of the sensitivity of the reversed reaction with that of the passive transfer reaction (Prausnitz and Küstner) revealed that the reversed reaction is still strongly positive at levels of antigen and antibody concentration at which the passive transfer reaction begins to fail.

Histamine Release in the Allergic Skin Reaction. Katz, Gerhard: Proc. Soc. Exper. Biol. & Med. **49**: 272, 1942.

An ingenious method was devised to demonstrate that histamine is released in the allergic skin reaction. A cantharides blister was produced on the chest or upper arm of a number of ragweed hay fever patients. The dead skin was removed, and an inverted funnel with the stem cut off was fastened over the denuded area. Locke's solution, which was introduced into the funnel, was changed at regular intervals and the samples were assayed for their histamine content by biologic and chemical means. After control samples had been taken, from 0.03 to 0.05 ml. of ragweed extract in saline was injected into the denuded skin area. Subsequent samples of the saline bath showed a rise in histamine content when a strong reaction occurred in the denuded area. The histamine content of the saline bath began to rise within ten minutes after the introduction of the allergen into the skin, reached its

height within thirty minutes, and dropped to the original level within one hour. An increased fluid exudation from the denuded area accompanied the histamine release. A "slow reacting substance" which produced a slow contraction of the atropinized guinea pig's ileum and temporarily diminished the histamine sensitivity of this organ was also present in the saline washing. In two treated cases of hay fever, the introduction of ragweed extract into the denuded area failed to produce a skin reaction and the associated release of histamine.

Peptone Shock in Rabbits. Gotzl, F. R., and Dragstedt, C. A.: J. Pharmacol. & Exper. Therap. **74:** 33, 1942.

Because of the similarity between peptone shock and anaphylaxis in rabbits, the changes which occur in the concentration of histamine in the blood and plasma in peptone shock were studied. Anaphylactic shock in rabbits is characterized by a marked leucopenia and a decrease in total blood histamine. The addition of antigen to the blood of sensitized rabbits, in vitro, produces a release of histamine from the blood cells to the plasma.

The intravenous injection of proteoses in rabbits produced a marked reduction in blood histamine and a moderate leucopenia. The addition of peptone to heparinized blood of normal rabbits caused a release of histamine from the blood cells to the plasma. Therefore, the effects of peptone shock upon the total blood histamine and upon the white blood cell count in rabbits are similar to those observed following anaphylaxis in the same animal. However, the general symptoms following the injection of peptone into rabbits were not so severe as those occurring during anaphylaxis.

Experimental Focal Necrosis of the Liver. Hartley, G., Jr., and Lushbaugh, B. S.: Am. J. Path. **18:** 323, 1942.

In an effort to determine whether thrombosis or the direct action of toxic substances, or both, were responsible for the focal necrosis of the liver, which is commonly observed in infectious and toxic diseases, the authors induced lesions of this type, experimentally, in hypersensitive animals.

Rabbits and guinea pigs were sensitized to crystalline egg albumin. The antigen was then injected into the mesenteric veins, the marginal ear veins, the abdominal cavity, and the spleen. Those animals which survived the anaphylactic shock were sacrificed, at varying times, following the injection of the antigen. Specimens of liver tissue were taken at the time of the first operation and after the animals were killed.

Rabbits sensitized with crystalline egg albumin showed large areas of coagulated necrosis of the liver parenchyma, following the injection of the antigen into the peritoneal cavity, into the spleen, or into the mesenteric or marginal ear veins. Control groups treated with nonrelated antigen failed to show these lesions. Sensitized guinea pigs, which received injections of crystalline egg albumin into the mesenteric veins, showed similar hepatic lesions. Vascular thrombosis was rarely present and apparently was secondary to necrosis of the hepatic cells. The portal veins and the sinusoids showed polymorphonuclear congestion prior to the onset of necrosis of the liver. In the interlobular lesions there was no evidence of hemorrhage, edema, or change in the vascular endothelium. It was concluded that focal necrosis of the liver was a direct result of the local union of antigen and antibody. The coagulative necrosis, the leucocytic response, and the infrequent thrombosis of the adjacent blood vessels were regarded as secondary to the antigen-antibody reaction.

The Influence of Artificial Fever on Mechanisms of Resistance. Ellingson, H. V., and Clark, P. F.: J. Immunol. **43**: 65, 1942.

Rabbits under the influence of artificial fever were immunized, both actively and passively, with various antigens, in an effort to determine the effect of elevated temperatures upon the mechanism of immunity.

Antibody titers of heated and control groups were compared. Artificial fever was induced during or after immunization. The antigens employed for immunization were crystalline egg albumin, typhoid vaccine, and sheep red blood cells. The results indicated that in rabbits a fever of about 41.5° C., induced during active immunization, depresses antibody response, while a fever of about 40° C. has no effect. In passively immunized rabbits, a fever of about 41° C. hastens the drop in antibody titers. A fever of 41.6° C. in rabbits, previously immunized with killed typhoid organisms, produces an abrupt reduction in antibody titers. The titers may be maintained at a low level by the induction of fever for several hours each day. Artificial fever had little or no effect upon complement in rabbit serum. Fever, induced during intracutaneous infection with Type I pneumococci, failed to influence appreciably the subsequent course of the infection. Phagocytosis of staphylococci, by leucocytes in either human or guinea pig blood, was enhanced by elevated temperatures.

Pediatrics

UNDER THE DIRECTION OF WILLIAM C. DEAMER, M.D., SAN FRANCISCO

Calsoy: A Soybean Substitute for Milk. Feingold, B.: J. Pediat. **20**: 485, 1942.

Directions for making an inexpensive soybean milk substitute suitable for home or hospital use are given. The product can be kept for a week if properly stored in a cold place. It has about twice the protein and less than half the carbohydrate content of cow's milk.

The protein composition of cow's milk that is usually accepted is higher than the author indicates in the report.

Bronchoscopic Aspects of Asthma in Children. Van Loon, E. L., and Diamond, S.: Am. J. Dis. Child. **63**: 217, 1942.

One hundred children with chronic allergic asthma were studied bronchoscopically. No evidence of bronchospasm or edema of the bronchi was found. The examination was conducted without anesthetic and was done at least twice on each patient. Most of the observations were done at intervals between attacks, although patients were also bronchoscoped during attacks for purposes of aspiration.

The most common finding was the presence of mucopurulent or thick mucoid secretion which was present in sixty patients. All the patients who were bronchoscoped during an attack had thick viscid intraluminal secretion, the aspiration of which in every instance diminished the severity of the attack and at times caused it to subside completely.

While 36 per cent of the children showed accentuation of the physiologic postero-anterior narrowing that occurs in the trachea and larger bronchi during expiration, it varied greatly in different children, and also in the same child it was not at all a constant finding. It was not found more often during the acute episodes. The patients in which asthma was of longer standing were less likely to show it.

Complete occlusion of a bronchus with resultant lobar or segmental atelectasis was not observed. In twenty cases the symptoms suggested the existence of bronchiectasis and bronchographic study was made. In five cases ectatic bronchi were outlined by this procedure.

The bacterial contents of material aspirated at successive bronchoscopies on the same patient were rarely alike.

The authors conclude that in the light of present knowledge it seems that the presence of thick mucoid secretion in the trachea and in the bronchi is intimately related to the creation of the respiratory disfunction but that an asthmatic attack must entail the operation of some other mechanical element in addition.

Rhinology and Ophthalmology

UNDER THE DIRECTION OF FRENCH K. HANSEL, M.D., ST. LOUIS

Nonsecreting Cysts of the Maxillary Sinus Mucosa. Lindsay, J. R.: Laryngoscope **52**: 84, 1942.

Lindsay has shown that nonsecreting cysts of the antrum are capable of producing a variety of symptoms such as fatigue, irritability, headaches, low-grade fever, mild dizziness, and pains in the joints. An x-ray examination is necessary to determine their presence. The cyst fluid is usually sterile in all ordinary culture media. Chemical analysis has shown that the cyst fluid must be classed as an exudate. He states that this fact suggests that these cysts are not caused by allergic reaction of the mucosa, since in all allergic reactions the resulting edema is a transudate and reversible.

Nasal Glands. Brunner, Hans: Arch. Otolaryng. **35**: 183, 1942.

Brunner presents a very comprehensive study of the various types of glands in the nasal epithelium. He states that the hyperactivity concerns chiefly the mucous glands and may lead to exhaustion, rupture of the gland, or formation of cysts, or eventually to atrophy. He points out that the cysts may originate in the gland tubules, the excretory tubes, or in the crypts. The first evidence of the effect exerted on the glands by the edema of nasal polyps is the complete or almost complete cessation of the production of mucus in the epithelium as well as in the glands. Purulent as well as hyperplastic inflammation of the nasal mucous membrane leads to atrophy and necrosis of the nasal glands, the first by toxins and the second by dysfunction of the glands. He also points out that the same dysfunction of glands has been found by other investigators in the bronchial mucous membrane of patients who succumbed to bronchial asthma and in the salivary glands after dissection of the secretory nerves.

The Presence and Action of Lysozyme in the Nasal Mucosa. Cahn-Bronner, C. E.: Ann. Otol., Rhin. & Laryng. **51**: 250, 1942.

In studying the presence and action of lysozyme in the nasal mucosa, Cahn-Bronner confirmed the observations of Fleming and Hilding in noting that lysozyme disappeared or decreased heavily during the first two days of a common cold. It is noteworthy that the discharge from running noses of hay fever patients showed a high lysozyme content. He states, however, that the absence of lysozyme cannot be considered as proof of a causal connection between this affection and lysozyme.

2-Amino-Heptane Sulfate as a Nasal Vasoconstrictor. Proetz, Arthur W.: Ann. Otol., Rhin. & Laryng. **51**: 112, 1942.

Proetz presents his observations on a new nasal vasoconstrictor, 2-amino-heptane sulfate. Among 119 applications of the drug, there were no complaints from any of the patients as to untoward reactions. Compared with a 2 per cent isotonic aqueous solution of ephedrine sulfate, 2 per cent 2-amino-heptane sulfate brought about much greater constriction and a more pronounced ischemia. The 1 per cent solution also showed greater constrictive effect than the 2 per cent ephedrine in every case. The 0.5 per cent solution of 2-amino-heptane sulfate approximated in its effect the 2 per cent ephedrine solution. In only three of the fifty-seven cases was the ephedrine definitely more active. In general the latent period preceding the constriction was somewhat longer than that of the ephedrine. The following concentrations of 2-amino-heptane sulfate were suggested: in atomizers, 0.5 per cent and 1 per cent, respectively, for routine shrinking, the choice depending upon the nasal response; in bottles, 2 per cent solution to be applied on cotton pledgets in cases requiring greater constriction for examination or for hemostasis. A 0.2 per cent solution is recommended for displacement.

Allergy in Relation to Otolaryngology. Kuhn, H. A., and Linton, L. D.: Ann. Otol., Rhin. & Laryng. **51**: 162, 1942.

Kuhn and Linton, in a review of 3,657 consecutive cases in eye, ear, nose, and throat practice, noted that 20 per cent of the cases had nasal complaints. A review of this 20 per cent or 720 nasal cases showed 140 allergic nasal cases, or 19.4 per cent. Other than allergic nasal cases there were 580, or 80.6 per cent. The allergic nasal cases constituted 3.7 per cent of all those reviewed. From their observations they concluded that the frequency of allergy as a complicating factor in otolaryngology should be appreciated. It is emphasized that the search for eosinophiles is not reliable unless the search is continued over a period of time in some cases. Allergic investigation and management is an important therapeutic adjunct to surgical and medical management.

Correspondence

The Editor,
THE JOURNAL OF ALLERGY.

Apropos of a letter by Dr. Unger published on page 326 of the March, 1942, issue of THE JOURNAL OF ALLERGY, may I state that I have been experimenting with the dextrose-extracting fluid ever since it was first introduced by Moore and Unger. Their modification of the original formula by increasing the phenol content from 0.1 per cent to 0.5 per cent and the addition of a sodium bicarbonate buffer was a distinct improvement. Innumerable tests, however, have demonstrated to my complete satisfaction that pollen extracts prepared with the dextrose-extracting fluid are definitely less stable than those prepared with glycerin. Furthermore, dextrose pollen extracts are subject to contamination with fungi, whereas extracts containing anywhere from 46 to 66 per cent glycerin have remained consistently sterile.

The slight pain that is produced by the injection of glycerin extracts has been greatly exaggerated by some of the advocates of aqueous (saline or dextrose) extracts. Another point worth mentioning is that glycerin extracts are absorbed more slowly from the tissues, and hence are less likely to cause constitutional reactions.

Finally, my results from treatment with dextrose pollen extracts have been definitely inferior to those obtained with glycerin extracts.

GRAFTON TYLER BROWN.

Washington, D. C., March 25, 1942.